

BMJ Open

Can Promoting Awareness of Fetal movements and Focussing Interventions Reduce Fetal Mortality? - A stepped wedge cluster randomised trial (AFFIRM)

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2016-014813
Article Type:	Protocol
Date Submitted by the Author:	21-Oct-2016
Complete List of Authors:	<p>Heazell, Alexander; University of Manchester, Maternal and Fetal Health Research Centre</p> <p>Weir, Christopher; University of Edinburgh, MRC Hub for Trials Methodology Research; Edinburgh Clinical Trials Unit</p> <p>Stock, Sarah; Queen's Medical Research Institute, EH16 4TJ, Tommy's Centre for Maternal and Fetal Health, MRC Centre for Reproductive Health,; School of Women's and Infants' Health, University of Western Australia, Crawley WA 6009. (FMM)</p> <p>Calderwood, Catherine; The Scottish Government St Andrew's House, EH1 3DG., Chief Medical Officer for Scotland,</p> <p>CunninghamBurley, Sarah; University of Edinburgh, Public Health Sciences</p> <p>Froen, Frederik; Nasjonalt folkehelseinstitutt, Division of Epidemiology</p> <p>Geary, Michael; Rotunda Hospital, Parnell Square</p> <p>Hunter, Alyson; Royal Maternity Hospital, Grosvenor Road, BT12 6BB</p> <p>McAuliffe, Fionnuala; University College Dublin,</p> <p>Murdoch, Edile; Royal Infirmary of Edinburgh, NHS Lothian, EH16 4SA., Department of Neonatology</p> <p>Rodriguez, Aryelly; University of Edinburgh, (ECTU) Edinburgh Clinical Trials Unit</p> <p>Ross-Davie, Mary; NHS Education for Scotland, 3rd Floor, Hanover Buildings, 66 Rose Street, EH2 2NN.</p> <p>Scott, Janet; Sands, Victoria Charity Centre, Suite GF2 Ground Floor, 11 Belgrave Road, SW1V 1RB.</p> <p>Whyte, Sonia; Queen's Medical Research Institute, EH16 4TJ, Tommy's Centre for Maternal and Fetal Health, MRC Centre for Reproductive Health,</p> <p>Norman, Jane; , Queen's Medical Research Institute, EH16 4TJ</p>
Primary Subject Heading:	Obstetrics and gynaecology
Secondary Subject Heading:	Research methods
Keywords:	Reduced Fetal Movements, Perinatal Mortality, Stillbirth, Neonatal Death, Fetal Growth Restriction

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

1 Study Protocol

2 Can Promoting Awareness of Fetal movements and Focussing Interventions Reduce
3 Fetal Mortality? - A stepped wedge cluster randomised trial (AFFIRM)

4 Alexander E P HEAZELL,^{1,2} alexander.heazell@manchester.ac.uk

5 Christopher J WEIR,^{3,4} christopher.weir@ed.ac.uk

6 Sarah J E STOCK,^{5,6} sarah.stock@ed.ac.uk

7 Catherine J CALDERWOOD,⁷ catherine.calderwood@scotland.gsi.gov.uk

8 Sarah CUNNINGHAM-BURLEY,⁴ sarah.c.burley@ed.ac.uk

9 J Frederik FROEN,⁸ frederik.froen@fhi.no

10 Michael GEARY,⁹ mppgeary@gmail.com

11 Alyson HUNTER,¹⁰ alyson.hunter@belfasttrust.hscni.net

12 Fionnuala M MCAULIFFE,¹¹ fionnuala.mcauliffe@ucd.ie

13 Edile MURDOCH,¹² edile.murdoch@nhslothian.scot.nhs.uk

14 Aryelly RODRIGUEZ,^{3,4} aryelly.rodriguez@ed.ac.uk

15 Mary ROSS-DAVIE,¹³ mary.ross-davie@nes.scot.nhs.uk

16 Janet SCOTT¹⁴ janet.scott@uk-sands.org

17 Sonia WHYTE⁵ sonia.whyte@ed.ac.uk

18 Jane E NORMAN.⁵ jane.norman@ed.ac.uk

19

20 1. Maternal and Fetal Health Research Centre, Institute of Human Development,
21 University of Manchester. 2. St. Mary's Hospital, Central Manchester University
22 Hospitals NHS Foundation Trust, Manchester Academic Health Science Centre,
23 Manchester, M13 9WL. 3. Edinburgh Clinical Trials Unit, Edinburgh, UK 4. Centre for

24 Population Health Sciences, Usher Institute of Population Health Sciences and
25 Informatics, University of Edinburgh, Teviot Place, Edinburgh EH8 9AG. 5. Tommy's
26 Centre for Maternal and Fetal Health, MRC Centre for Reproductive Health, Queen's
27 Medical Research Institute, Edinburgh, EH16 4TJ.6. School of Women's and Infants'
28 Health, University of Western Australia, Crawley WA 6009. (FMM) 7. Chief Medical
29 Officer for Scotland, The Scottish Government St Andrew's House Edinburgh EH1
30 3DG. 8. Department of International Public Health, Norwegian Institute of Public
31 Health, PB 4404 Nydalen, N-0403 Oslo, Norway, 9. Rotunda Hospital, Parnell
32 Square, Dublin 1, Ireland. 10. Centre for Fetal Medicine, Royal Maternity Hospital,
33 Grosvenor Road, Belfast, BT12 6BB 11. UCD Obstetrics & Gynaecology, School of
34 Medicine, University College Dublin, Ireland. National Maternity Hospital, Dublin,
35 Ireland. 12. Department of Neonatology, Royal Infirmary of Edinburgh, NHS Lothian,
36 Edinburgh, EH16 4SA. 13. NHS Education for Scotland, 3rd Floor, Hanover
37 Buildings, 66 Rose Street, Edinburgh EH2 2NN. 14. Sands, Victoria Charity Centre,
38 Suite GF2 Ground Floor, 11 Belgrave Road, London, SW1V 1RB.

39

Abstract

Background - In 2013, the stillbirth rate in the UK was 4.2 per 1,000 live births, ranking 24th out of 49 high-income countries, with an annual rate of reduction of only 1.4% per year. The majority of stillbirths occur in normally formed infants, with (retrospective) evidence of placental insufficiency the commonest clinical finding. Maternal perception of reduced fetal movements (RFM) is associated with placental insufficiency and increased risk of subsequent stillbirth.

This study will test the hypothesis that the introduction of a package of care to increase women's awareness of the need for prompt reporting of RFM and standardised management to identify fetal compromise with timely delivery in confirmed cases, will reduce the rate of stillbirth. Following the introduction of a similar intervention in Norway the odds of stillbirth fell by 30%, but the efficacy of this intervention (and possible adverse effects and implications for service delivery) have not been tested in a randomised trial.

Methods - We describe a stepped wedge cluster trial design, in which participating hospitals in the UK and Ireland will be randomized to the timing of introduction of the care package. Outcomes (including the primary outcome of stillbirth) will be derived from detailed routinely collected maternity data, allowing us to robustly test our hypothesis. The degree of implementation of the intervention will be assessed in each site. A nested qualitative study will examine the acceptability of the intervention to patients and health care providers and identify process issues including barriers to implementation.

Discussion - The data provided by this study will inform the management of women with RFM; which has been recurrently identified as suboptimal in cases of stillbirth. This will provide robust evidence to determine whether increased maternal awareness of RFM combined with a standardised management protocol to identify acute or chronic fetal compromise can reduce stillbirth.

67 *Trial Registration*

68 www.clinicaltrials.gov NCT01777022

69 *Version*

70 Protocol Version 4.1, 18th October 2016

71 *Keywords*

72 Reduced Fetal Movements; Perinatal Mortality; Stillbirth; Neonatal Death; Fetal
73 Growth Restriction.

74

75 **STRENGTHS AND LIMITATIONS OF THIS STUDY**

- 76 • This trial directly addresses the need for studies of the information given to
77 women regarding fetal movements and the subsequent management of reduced
78 fetal movements identified by Confidential Enquiries into Antepartum Stillbirths,
79 Systematic Reviews and the Stillbirth Priority Setting Partnership.
- 80 • A stepped-wedge cluster trial design in combination with routinely collected
81 maternity data allows the trial to be adequately powered to detect a difference in
82 stillbirth as a primary outcome.
- 83 • The pragmatic nature of the study represents the potential impact of the
84 introduction of such standardised care into clinical practice.
- 85 • The nested qualitative study will provide information regarding the acceptability
86 of the intervention and identify barriers and facilitators to its adoption.
- 87 • The lack of information on resource use before and throughout the study period
88 limits the ability to understand the consequences of the intervention on maternity
89 unit workload.

90

91

92 INTRODUCTION

93 *Stillbirth*

94 Stillbirth, defined in the UK as a baby with no signs of life after 24 weeks of completed
95 pregnancy ¹, remains the major cause of perinatal mortality in high-income
96 environments, with a recent series of papers in the Lancet on stillbirth issue calling for
97 renewed action in this area ². There is no single “cause” of stillbirth, and a significant
98 proportion of stillbirths remain unexplained, but fetal growth restriction, maternal
99 hypertension and low socioeconomic status are amongst the identifiable risk factors ³.

100 The concept that more can be done to reduce stillbirth in the UK and Ireland is
101 supported by data showing a marked variation in rates between resource rich
102 countries, when similar definitions of stillbirth are used ². Notably, the UK has a higher
103 rate than comparable resource rich countries such as Germany, Netherlands, New
104 Zealand and Norway with rates in the UK some 50% greater than those of the
105 Netherlands. Disappointingly, the annual rate of reduction in stillbirth from 2000 to
106 2014 in the UK was only 1.4% compared to 6.8% in the Netherlands and 2.8% in New
107 Zealand ². Rates of stillbirth in Scotland (3.7 per 1,000 births in 2014) and Ireland, at
108 (4.4 per 1,000 livebirths in 2013) are similar to rates in England and Wales at 4.2 per
109 1,000 livebirths (England and Wales, 2014) ⁴. The reduction of avoidable harm for
110 women and babies is viewed as a major priority for Government and its agencies
111 throughout the UK and Ireland. Consequently, several initiatives have been
112 developed by national governments in the UK and Ireland including the Scottish
113 Government Stillbirth Working Group, NHS England Saving Babies’ Lives Care
114 Bundle and the Welsh Assembly 1000 Lives Plus strategy. These strategies have
115 identified the need for better evidence to guide efforts to prevent stillbirths.

116 Using a robust priority setting strategy ⁵ the Lancet Stillbirth’s series steering
117 committee identified issues around detection and management of reduced fetal
118 movements (RFM) amongst the top ten key research questions on prevention and

management of stillbirth⁶. This was confirmed in the UK-based Stillbirth Priority Setting partnership involving over 1,700 parents and professionals which identified two relevant issues among the highest ranked research questions regarding stillbirth: i) which investigations identify a fetus at risk of stillbirth after a mother believes she has experienced reduced fetal movements? and ii) would more accessible evidence-based information on signs and symptoms of stillbirth risk, designed to empower women to raise concerns with healthcare professionals, reduce the incidence of stillbirth?⁷ Thus, RFM has been identified as a highly-relevant area of study by parents, professionals and researchers.

Reduced Fetal Movements, Stillbirth and Placental Insufficiency

There is a clear association between maternal perception of RFM and late stillbirth dating back over four decades⁸. In a recent series of 2,000 women, the adjusted OR (95% CI) of late stillbirth in women with RFM (compared with controls) was 2.37 (1.29-4.35)⁹. One international study of 1,714 women who experienced a stillbirth found that 30% had noted significant RFM prior to the diagnosis of stillbirth¹⁰. Although the mechanisms have not been fully delineated, it is likely that RFM and stillbirth are linked by a common pathology, that of placental dysfunction¹¹. There is good evidence linking placental dysfunction and RFM. Women who have fewer fetal movements on ultrasound immediately prior to caesarean section are more likely to have umbilical cord gas measurements indicative of acidaemia, hypoxaemia, and hypercapnia, compared with controls¹². Women delivering within one week of an episode of RFM show differences in placental structure and function which are reminiscent of those seen in fetal growth restriction (FGR) and stillbirth¹³. Additionally, the odds of fetal growth restriction (FGR, defined as being at less than the 10th centile for gestation adjusted birthweight) were greater in women with RFM compared with controls (adjusted OR 1.6, 95% CI 1.1–2.2¹⁴). Taken together these

1
2
3 146 data are strong evidence that placental dysfunction is associated with RFM, and a
4
5 147 causative pathway seems likely.
6

7 148 The evidence linking placental dysfunction and stillbirth is even stronger; a systematic
8
9 149 review of placental pathology in stillbirths described abnormalities in up to 65% of
10
11 150 cases ¹⁵. Amongst the 291 stillbirths in Scotland in 2010, 137 (47%) had evidence of
12
13 151 placental dysfunction ¹⁶. Given that the placenta was examined in only 80% of
14
15 152 stillbirths, the true prevalence of placental dysfunction is likely to be higher. In
16
17 153 addition, between 20%-40% of stillborn babies are reported to have FGR, as defined
18
19 154 by a birthweight less than the 10th centile ¹⁷. Additionally, the Lancet report notes that
20
21 155 “placental pathologies accounted for one in four deaths across all gestational ages,
22
23 156 and were contributory or causal in more than half of cases” ⁶. Given that stillbirth is
24
25 157 strongly related to placental dysfunction, and RFM is a “biomarker” of placental
26
27 158 dysfunction then better management of women presenting with RFM focussing on the
28
29 159 detection of placental dysfunction might reduce the risk of stillbirth.
30
31

32 160

33 161 *Formal Fetal Movement Counting*

34
35 162 Although prenatal detection of FGR is improved by fetal movement counting ¹⁸, a
36
37 163 systematic review ¹⁹, and a large and influential cluster randomised trial (which
38
39 164 dominates the systematic review) showed that routine fetal movement counting using
40
41 165 the count to ten charts had no effect on perinatal mortality ²⁰. Thus, the National
42
43 166 Institute for Health and Social Care Excellence (NICE) recommended that “Routine
44
45 167 formal fetal movement counting should not be offered” ²¹. Importantly, the large
46
47 168 cluster randomised trial tested a specific alarm limit for RFM, but did not recommend
48
49 169 a specific management strategy for women who did present with RFM. There were
50
51 170 two important observations from this study, firstly that in both groups the perinatal
52
53 171 mortality rate was lower than contemporary or subsequent periods in the UK and
54
55 172 secondly that more women in the fetal movement counting arm came in with a live
56
57 173 baby who subsequently died compared with the control arm (19 vs 11), suggesting
58
59
60

174 that one reason the strategy failed to reduce perinatal mortality was inadequate
175 investigation and management of those presenting with RFM ²⁰.

176

177 *Efficacy of a package of intervention for RFM*

178 Supportive data for the package of interventions used in this study comes from a
179 large observational “clinical quality improvement study” in Norway which found a
180 significant fall in rates of stillbirth (from 3.0/1,000 to 2.0/1,000 [OR 0.67 95% CI 0.48–
181 0.93]) after the introduction of an intervention package consisting of written
182 information for women about awareness of RFM combined with consensus guidelines
183 for health professionals about their management ²². Although this study was not
184 randomised, and therefore constitutes only level II-3 evidence, it has informed
185 recommendations from the Royal College of Obstetricians and Gynaecologists
186 (RCOG) and Perinatal Society of Australia and New Zealand (PSANZ) that “women
187 should be advised to be aware of their baby’s individual pattern of movements and
188 that if they are concerned about a reduction in or cessation of fetal movements
189they should contact their maternity unit” ^{23 24}. Following initial publication of the
190 Norwegian study, a re-analysis was required as discrepancies between stillbirth rates
191 in the study and the Medical Birth Registry of Norway were identified. This reanalysis
192 found the reduction in stillbirth rates was of borderline statistical significance (OR
193 0.72, 95% CI 0.50-1.03). The authors concluded that further studies were needed to
194 determine whether this approach was associated with a reduction in stillbirth ²⁵.

195 Importantly, in the Norwegian study, there was no increase in the proportion of
196 women who presented with RFM when rates were compared before and after the
197 intervention ²². However, women with RFM presented significantly earlier to hospital
198 than they had hitherto, potentially allowing time for intervention to reduce perinatal
199 mortality. These data suggest that a package of interventions encouraging women
200 with RFM to present early to hospital, combined with a structured approach to their
201 management might reduce rates of stillbirth without contributing to a large increase in

admissions antenatally.

203

204 *Optimal strategy for determining RFM*

205 There is no uniform threshold of fetal movements below which perinatal morbidity
206 increases ²⁶, and no evidence that a specific threshold performs better than maternal
207 perception of reduced fetal movements alone ⁸. Therefore, guidelines from the RCOG
208 and PSANZ ^{23 24}, informed by the Norwegian study ²² suggest that it is maternal
209 *perception* of decreased fetal movement which is important.

210

211 *Optimal strategy for investigation and management of women presenting with RFM.*

212 A recent systematic review found there are no proven strategies for the investigation
213 and management of women presenting with RFM ²⁷. Cardiotocography (CTG) is
214 routinely used to ascertain fetal wellbeing, and it is the cornerstone of the RCOG
215 guideline ²⁴. However, data from Norway, suggests that ultrasound assessment of
216 fetal size is often the most helpful investigation, performing well on both an absolute
217 basis, and compared with other interventions ²⁸. In a series of over 3,000 women with
218 RFM, ultrasound (including measurement of fetal biometry and liquor volume) was
219 found to be useful in detecting abnormalities in 11.6% of scans. In 71% of women in
220 whom an abnormality was found, ultrasound was the only technique that detected an
221 abnormality. Additionally, 85% of abnormalities detected by ultrasound, were
222 important in informing the clinical management of the woman ²⁸. These data are
223 supported by a smaller UK study which found that abnormalities detected on CTG or
224 ultrasound scan were most strongly associated with adverse outcome in women with
225 RFM, with identification of abnormal estimated fetal growth centile on scan being the
226 test most highly predictive of poor outcome ²⁹. Perhaps this is not surprising, given the
227 strong association between RFM and placental dysfunction and the central
228 importance of ultrasound in the identification and management of small for gestational
229 age babies ³⁰. Given these data, it is concerning that a survey of clinicians in Scotland

showed that fewer than 5% would routinely refer women with RFM for ultrasound examination (unpublished data from June 2012), and a survey of 223 UK midwives and obstetricians described that 17.9% of respondents would perform an ultrasound scan³¹. These views of clinicians may reflect the variable quality of local guidelines, which are frequently not based on national recommendations, even those for which there is strong evidence³². The variation in information given to women and subsequent management of RFM has been highlighted as sources of suboptimal care in two confidential enquiries into antepartum stillbirth^{33 34}. Therefore, we believe that current investigation of women presenting with RFM is inadequate, hence using the best available evidence, we have drafted what we consider to be a robust evaluation protocol for investigation of women with RFM.

241

Potential harms of a package of care around increased awareness and optimised management of RFM

Any clinical intervention which aims to improve outcomes also has the ability to do harm. Thus, it is essential that the intervention proposed is rigorously evaluated using the gold standard technique of a randomised trial, rather than being introduced as a service development. When the study began, there was a small window of opportunity to do this, as the enthusiasm to improve current management of RFM is such that routine introduction of the package of care is unlikely to be delayed much further than the current scheduled end date of this study. Possible harms of a package of care consisting of a management plan for identification and delivery of the “at risk” fetus, together with strategies for increasing pregnant women’s awareness of the need to report early include increased maternal anxiety and increased intervention (including hospital admission, induction of labour and Caesarean section) which itself is associated with pregnancy related complications. The available evidence is reassuring on some of these issues. Encouraging women to be aware of

1
2
3 257 fetal movement does not increase maternal anxiety ³⁵, and it appears to have a
4
5 258 neutral effect on maternal- infant attachment ³⁶. In the Norwegian service
6
7 259 development study, the package of care increased rates of follow up of women, but
8
9 260 there was no increase in admissions overall, admissions for induction or admissions
10
11 261 for emergency caesarean section ²² – again, whilst reassuring these outcomes
12
13 262 require formal evaluation in a randomised and relevant setting to the UK and Republic
14
15 263 of Ireland. The final possible harm of the package is around increased resource use,
16
17 264 and the opportunity cost of focussing on RFM rather than other potential methods to
18
19 265 prevent stillbirth.
20

21
22 266

23 24 267 **RATIONALE**

25
26
27 268 The aim of this study is to test the hypothesis that a package of interventions
28
29 269 consisting of strategies for increasing pregnant women's awareness of the need to
30
31 270 report early when they perceive a reduction in fetal movements, followed with a
32
33 271 management plan for identification and delivery of the "at risk" fetus in such women,
34
35 272 will reduce rates of stillbirth.
36

37
38 273

39 40 274 **STUDY OBJECTIVES**

41 42 275 *Primary Objective*

43
44
45 276 The primary objective is to answer the research question 'Does the introduction of a
46
47 277 protocol for detection and management of decreased fetal movements reduce rates
48
49 278 of stillbirth?' The secondary objectives are to answer the following research
50
51 279 questions:

- 52
53
54 280 • What is the effect of the intervention on rates of caesarean section and induction
55
56 281 of labour?
57
58
59
60

- 282 • What is the effect of the intervention on rates of admission to the neonatal
283 intensive care unit?
- 284 • What is the effect of the intervention on the proportion of women with FGR
285 remaining undelivered by 40 weeks gestation?
- 286 • What is the acceptability of such a package of care to pregnant women and their
287 health care providers?
- 288 • What other process outcomes are influenced by the intervention, such as health
289 care provider/patient interactions?

290

291 **ENDPOINTS**

292 *Primary Outcome*

293 The primary endpoint is stillbirth (antepartum and intrapartum). We will use the UK
294 definition of stillbirth which is “a baby delivered without signs of life after 23⁺⁶ weeks”
295 ⁴. Where gestation is uncertain we will include all babies with a birth weight of 500g
296 or more.

297 *Secondary Endpoints*

298 Other measures of perinatal mortality including:

- 299 • Stillbirth at 28 weeks gestation and above (WHO definition of stillbirth)
- 300 • Stillbirth at 22 weeks gestation and above (international stillbirth alliance
301 definition)
- 302 • Stillbirths amongst normally formed infants of 22 weeks gestation and above,
303 24 weeks gestation and above and 28 weeks gestation and above
- 304 • Perinatal mortality (defined as stillbirth at 24 weeks gestation and above and
305 deaths in the first seven days of life)
- 306 • Rates of caesarean section

- 307 • Rates of induction of labour
- 308 • Rates of admission to the neonatal intensive care unit (and their reasons)
- 309 • Rates of admission to the neonatal intensive care unit for more than 48 hours
- 310 • Proportion of infants with fetal growth restriction (less than the 10th centile,
311 customised for gender) remaining undelivered at or after 40 weeks gestation
- 312 • Birthweight centile (according to <https://www.gestation.net>)
- 313 • Rates of spontaneous vaginal delivery

314 We will also collect the following data to allow adjustment for these variables:
315 maternal age, maternity unit of delivery, birthweight, gestation of delivery, parity,
316 gestation, sex, smoking (current and ever), maternal body mass index (BMI), number
317 of babies (one or more), ethnicity (to allow a customised birthweight centile to be
318 generated), method of delivery, deprivation category (where available) and other
319 neonatal variables including Apgar score and encephalopathy.

320

321 **STUDY DESIGN**

322 This is a multicentre, stepped wedge cluster randomised trial of a package of care
323 consisting of a management plan for identification and delivery of the 'at risk' fetus,
324 together with strategies for increasing pregnant women's awareness of the need to
325 report RFM early. The study will take place in participating hospitals in the UK and
326 Ireland (a complete list is available [http://www.crh.ed.ac.uk/affirm/randomised-](http://www.crh.ed.ac.uk/affirm/randomised-hospitals/)
327 [hospitals/](http://www.crh.ed.ac.uk/affirm/randomised-hospitals/)). A nested qualitative study will examine the acceptability of the
328 intervention to patients and health care providers and identify process issues
329 (barriers to implementation). Clinical audit conducted after the change in practice will
330 be used to determine the effect of interventions on process outcomes (e.g. number of
331 women presenting with reduced fetal movements, interval between perceiving

reduced fetal movements and presentation to hospital, number of ultrasound scans, number of admissions for induction of labour). A diagram indicating randomisation of hospital groupings in the stepped wedge design is shown in Figure 1.

The interventions will be introduced over a 33 month period. Data will be collected over a 36 month period. Data in the ‘active phase’ after introduction of the intervention will be compared to data in the ‘control phase’ – the period during which usual care processes in study sites are followed from study start to the time of introduction of the intervention. Given that it will take individual units some time (a) to effect change in management in their unit from time of introduction of the intervention and (b) that it will take some time for this change in practice to impact on clinical outcomes, we plan a “washout” period of two months after the introduction of the intervention during which data will not be included in either group for analysis.

STUDY POPULATION

Number of participants

Participants will be those delivering at all the sites over the study period (36 months). All eligible women will be recruited to the cluster randomised controlled trial. Based on previous delivery numbers, after accounting for a washout period of two months (and assuming no withdrawals or losses to follow up) this is estimated to be a total of around 143,140 women per annum. A subset of around 30 participating women and 30 midwives, sonographers and obstetricians will be recruited to the nested qualitative study, which is based in the Scottish sites.

Inclusion criteria

We will include all women delivering at one of the participating maternity units for the duration of the study. Women who have been seen at any of the maternity units but who deliver at home will not be included. The duration of the study will be 42 months

from the start of the trial (01/02/2014). For practical reasons, participants for the nested qualitative study will be recruited from the participating units in Scotland.

Exclusion criteria

We will exclude women as follows:

- Women for whom data on delivery outcomes is still unavailable four months after the date of delivery
- Women delivering in the “washout” period in each unit.

Members of the trial management group and participants who do not speak/understand English will be excluded from participating in the nested qualitative study.

Identifying participants

Women will be identified from those whose data is included in routine data returns from each unit. Potential participants for the nested qualitative study will be identified from those attending antenatal clinics in participating hospitals, and/or local staff.

Consenting participants

The main study is a stepped wedge cluster randomised trial of a package of care which would be introduced in many of the participating units regardless of whether the trial was on-going or not and the trial uses only routinely collected data on participants. The ethics committee indicated that formal individual patient consent is not necessary for the main trial. Participants in the nested qualitative study will be asked for individual consent.

Screening for eligibility

As participants are not directly recruited we will not perform any specific screening tests for this aspect of this project. Participants for the nested qualitative study will be: (i) Pregnant women attending hospitals who are participating in the main trial in

Scotland. Purposive sampling will ensure that the final sample set includes women who have and who have not experienced RFM, both before and after the introduction of the intervention; (ii) Hospital staff (including midwives, ultrasonographers and obstetricians/radiologists) working in participating hospitals in Scotland. There will be no specific screening tests for eligibility for the nested qualitative study, except that women who have experienced a stillbirth in the index pregnancy will not be approached.

Ineligible and non-recruited participants

Potential participants for the nested qualitative study who are not approached or who decline will have no specific interventions / procedures.

Withdrawal of Study Participants

The nature of a cluster randomised study is such that it is not possible for the participant to withdraw from the “cluster” unless she changes maternity unit part way through her pregnancy. We plan to collect routinely recorded anonymised data; patients have the right to opt out of having their data used – if this happens their data would be excluded from the study database (e.g. under the Confidentiality and Security advisory Group Report 2002 and the Data Protection Act (1998) requirements for fair processing of data). Participants in the nested qualitative study who wish to withdraw will be allowed to do so. Their data will be retained and used, unless they additionally indicate that they wish to withdraw their data.

RANDOMISATION

Randomisation Procedures

This is a cluster-randomised, stepped-wedge design trial wherein maternity units rather than individual patients are randomised. All units will implement the fetal movement monitoring intervention at some point during the trial; the random element is the time point at which this will occur, the so-called “step” of the stepped-wedge

design. Participating maternity units will be blinded to their randomly allocated time point until the time this is required to be revealed to enable the necessary training in the implementation of the intervention to be delivered. Primary and secondary outcomes of the trial will be gathered in a blinded manner via routinely collected data sources.

Groups of units which are in close proximity to each other will be treated as strata for the purposes of randomisation. This will assist with the feasibility of delivering the training for and implementation of the intervention. Furthermore, this local synchronisation of the intervention implementation will minimise the chances of contamination (introduction of the intervention prematurely) from maternity units which have already implemented the intervention to those not yet randomised.

The order in which the strata of units step in to implement the intervention will be determined by computer generated random numbers from a uniform distribution. The randomisation list will be held by the Edinburgh Clinical Trials Unit (ECTU). The identities of the research team staff whose roles in the trial require them to be unblinded to randomisation codes will be recorded in the trial master file (TMF).

Treatment Allocation

Participating sites will be randomised to the intervention or conventional clinical management. All units will be providing conventional treatment at baseline according to local practice – this is the treatment established before the study starts. Sites will be randomised to “active” treatment in turn as described above. Active treatment will consist of a package of care consisting of a management plan for identification and delivery of the ‘at risk’ fetus, together with strategies for increasing pregnant women’s awareness of the need to report RFM early. The recommended management plan for identification and delivery of the “at risk” fetus is shown in Figure 2. Practice change in the active units will be achieved by: (i) written/email information to all clinicians (doctors, midwives and ultrasonographers) in each unit about the study protocol and

436 amendment of the local protocol for Reduced Fetal Movements (RFM) to that of the
437 study protocol; (ii) a short web-based training package taking approximately one hour
438 to complete for all clinicians in each centre and (iii) training /information sessions to
439 run in each unit and (iv) posters in each unit to describe the practice change.
440 Strategies for encouraging clinicians to increase pregnant women's awareness of
441 fetal movement will include all the above and also a fetal movement leaflet for
442 pregnant women (shown in Supplementary Information 1). Once units have begun
443 active treatment it is not anticipated that they will return to conventional treatment.
444 We will conduct an audit of women presenting with reduced fetal movements and
445 assess the proportion of staff completing the online training to assess the extent to
446 which sites have followed the intervention plan.

447 Units will be informed about treatment allocation as near as possible to the
448 implementation of the "active" treatment. For practical purposes, we anticipate that
449 each unit will need around three months' notice before the "active" treatment is
450 introduced, hence units will be informed of the timing of their treatment allocation
451 (step) three months before the active treatment is due to start. The treatment
452 allocation will not be administered blind and there are no restrictions on concomitant
453 care or other interventions during the study, hence there is no need for emergency
454 unblinding and there are no stopping rules for the study.

455 **DATA COLLECTION**

456 For the main trial, data will be accessed from the information routinely collected
457 during the clinical management of the patient. For consistency, we will normally only
458 include data items which become available within four months after the delivery date
459 in question, although we may seek advice from the independently-chaired trial
460 steering committee (TSC) about exceptions as they arise. Different data sources will
461 be used for different regions of the study: (i) In Scotland the source data will be
462 SMR2 and the Scottish Birth record, (ii) In Ireland the source data will be the National

Perinatal Reporting System (NRPS http://www.esri.ie/health_information/nprs), (iii) In Northern Ireland, the source data will be the Northern Ireland maternity Statistics database (NIMATS), (iv) In England and Wales, the source data will be the ONS, or other relevant body. Data will be collected retrospectively on an annual basis from all sources. We will assume that data unavailable four months after the woman delivered is likely to be unobtainable (but see note in Study Design section above). Thus, data on the first year of the study will be collected at month 16; data on the second year will be collected at month 28 etc.

Data are routinely collected. A formal request for data access will be made at the start of the study. This will require (i) in Scotland – Privacy Advisory Committee approval and a formal approach to NHS Scotland Information Services Division (ISD) (ii) in Ireland a formal approach to NRPS (iii) NIMATS in Northern Ireland (iv) in England and Wales a formal approach will be made to the relevant bodies.

Data will then be sent to the electronic Data Research and Innovation Service (eDRIS) National Safe Haven (NHS National Services Scotland) by secure file transfer protocol (or other similar) for storage and subsequent analysis within a secure project area (dedicated to the AFFIRM study). Further information on the National Safe Haven is available at <http://www.isdscotland.org/Products-and-Services/eDRIS/Becoming-an-eDRIS-User/#NSS-National-Safe-Haven>. Briefly, the National Safe Haven is located on a secure server, in which trusted and authorised researchers can analyse individual level data while maintaining the utmost confidentiality. It is anticipated that all study analysis will be done within the Safe Haven, using one of the available statistical packages (e.g. R, SPSS).

Identifiers on Scottish data within the National Safe Haven are concealed from researchers. Data from outwith Scotland will be anonymised before submission to the National Safe Haven. We propose that data submitted to the National Safe Haven will be “anonymised” by the data provider. However, we propose that the

anonymisation link will be retained at the source so that it will be possible to re-link data retrospectively. The rationale for retaining the ability of local data guardians to re-link data is because it is important to retain the possibility of identifying individual patients retrospectively. Examples include: (i) It is possible that some additional important data may be available at a late stage on individual participants – e.g. in the scenario where the woman or baby had a major adverse event and spent a long time in hospital before discharge or death and (ii) Although our protocol and outcome analysis does not require identifiable data, we believe this will be a ‘once in a lifetime’ study, and that subsequent secondary analyses could yield important information for patients and for policy makers. If retrospective identification is not possible, this will limit further analysis. One likely example of future analyses is to determine the effect of the intervention on different causes of stillbirth. This is outwith the scope of the current protocol, but could be done relatively straightforwardly, by linking nationally recorded information on “cause” of stillbirth to our study database. We anticipate that such additional analyses would require additional ethics approval, but without a process by which to re-link data, it will not be possible to perform such subsequent analyses.

All Investigators and study site staff involved with this study will comply with the requirements of the Data Protection Act 1998 (or equivalent for those outwith the UK) with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act’s core principles. Published results will not contain any personal data that could allow identification of an individual participant.

In addition to the data recorded above, all sites will be asked to provide a copy of their guidelines around (i) maternal awareness of RFM and (ii) management of women presenting with RFM. Copies of guidelines will be sought by the study office (a) at the start of the study (b) immediately before initiation of the intervention in each specific unit and (c) six months after initiation of the intervention in each specific unit.

For the nested qualitative study, we will perform interviews of healthcare workers and a small nested cohort of pregnant women about their experiences of fetal movement and of this intervention. We shall ensure a diversity of age and include nulliparous and multiparous women (n=30 in total). Ten interviews will be conducted with each of the following groups of health care providers: obstetricians, midwives and sonographers/radiologists. The interviews will take a semi-structured format (sensitising and piloting interviews will be conducted prior to the commencement of the trial and in the first month of the nested qualitative study). This format will ensure the same categories of data will be obtained from each participant but also allow individual responses to be fully explored.

STATISTICS AND DATA ANALYSIS

Sample size calculation

The sample size is the number of women delivering in hospitals participating in the study. This was initially planned to include sites in Scotland, totalling around 58,000 deliveries per year with 16 consultant led maternity units, 20 smaller units each delivering less than 350 babies per year, and seven units delivering less than five births per year. The units involved in Perinatal Ireland (an all-Ireland research consortium across 7 academic sites in Ireland currently funded by the Health Research Board, Ireland) have 50,000 births per year with seven large sites. Combining one or two of the smaller units and one larger unit into a single “hospital group” for each local area could provide 24 hospital “groups” – the details of hospital groupings will be reviewed and finalised immediately prior to randomisation. In total, 36 sites expressed interested in participating in the study, although 2 were unable to participate in the study and withdrew before randomisation. In total, 34 units were randomised, these were situated throughout the UK and Ireland (10 in England, 4 in Ireland, 15 in Scotland and 5 in Wales) with 143,140 births per annum.

We calculated statistical power using the methodology for stepped wedge designs proposed in Hussey and Hughes (2007)³⁷. First, we analysed stillbirth event data from the Scottish Perinatal and Infant Mortality and Morbidity Report (SPIMMR) covering years 2005-2010¹⁶ to determine estimates of between- and within-unit variability in stillbirth rate. Analysis was by generalized linear mixed model for binary outcomes. The power calculation, as per equations (#7) and (#8) in³⁷ assumed: significance level 5%; analysis by generalized linear mixed model; deliveries equally distributed across hospital groupings; baseline stillbirth rate 0.438%¹⁶; between-cluster variance 0.00816.

Finally, the statistical power depends on the number of groups in which the intervention is implemented at each stage of the stepped wedge design and the duration of recruitment at each “step”. Our study design proposes sequential introduction of the intervention into three hospital groups at a time at four month intervals over a 32 month period. It is anticipated that unavailability of data and women asking to withdraw their data will be less than 1%. This would give 89.9% power to detect a 30% relative risk reduction under the intervention and 77.0% power to detect a 25% reduction. A 30% risk reduction was seen in the Norwegian study; the anticipated effect sizes of 25% and 30% relative reduction take into account that the intervention will not have the power to reduce all stillbirths, since 20% of stillbirths in Ireland³⁸ and 15% in Scotland¹⁶ are associated with congenital anomaly.

Proposed analyses

For the binary primary and secondary outcomes, data will be analysed by generalized linear mixed model with a random effect for hospital and fixed effects for the intervention implementation, study time period and calendar year. A site by intervention interaction random effect will be included in the model and retained if it explains an important proportion of the variability in outcomes. The primary analysis of data will be on an intention to treat basis (the design of the trial means it is not

possible to determine individual patient /caregiver compliance with the intervention). An “on treatment” variable will be calculated for which women will be grouped as active or control according to when the intervention was actually implemented in their site, instead of when the site was randomised to implement the intervention. The primary outcome will be reanalysed using the “on treatment” classification in a sensitivity analysis. There are no planned imputations for missing data. However, if the missing data rate for smoking status during pregnancy is relatively high an imputation technique will be devised. The imputation method will be informed using smoking history at booking and age at delivery ³⁹. A pre-specified subgroup analysis will be performed for babies with and without congenital anomalies, and will be implemented by testing for an intervention by congenital anomaly interaction added to the generalised linear mixed model described above. No formal interim analyses for efficacy or safety will be performed. A full statistical analysis plan was finalised and signed on 05/10/2016.

Qualitative Data

For the nested qualitative study, the data will be audio recorded and transcribed. The data will be coded thematically and an analytical framework developed to make sense of patient experience of fetal movement and the intervention and also health care providers’ perspectives and experiences. NVivo will be utilised to support the analysis.

Process outcomes

The process outcomes being assessed by the (rates of induction of labour, number of women presenting with reduced fetal movements, interval between perceiving fetal movements and presenting to hospital) will be analysed using the same methods as for the main trial, with the exception of the continuous outcome (interval between perceiving fetal movements and presenting to hospital) which will be analysed using a normal linear mixed model.

ADVERSE EVENTS

This is not a Clinical Trial of an Investigational Medicinal Product (CTIMP) so adverse events will not be formally reported. Stillbirth and other measures of fetal and maternal morbidity are outcomes of the study. The purpose of the intervention is to reduce such adverse events. Therefore, due to the low risks for this trial, a separate DMC is not required and the Trial Steering Committee (TSC) will cover any responsibilities normally allocated to a DMC. If considered necessary, the TSC may review unblinded data for the study, including morbidity and mortality indices. No other adverse event reporting will be undertaken.

TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

The trial will be coordinated by a Project Management Group, consisting of the grant holders and the Trial Manager. The Chief Investigator (JN) will lead the project management group. The Trial Manager will oversee the study and will be accountable to the Chief Investigator. A TSC will be established to oversee the conduct and progress of the trial. The terms of reference and a draft template for reporting will be ratified in one of the early meetings of the TSC.

Investigators and institutions involved in the study will permit trial related monitoring and audits on behalf of the co-sponsors (ACCORD: Academic and Clinical Central Office for Research & Development - Joint office for University of Edinburgh and NHS Lothian, Sponsor contact: ray.french@ed.ac.uk), research ethics committee (REC) review, and regulatory inspection(s). In the event of an audit or monitoring, the Investigator agrees to allow the representatives of the sponsor direct access to all study records and source documentation. In the event of regulatory inspection, the Investigator agrees to allow inspectors direct access to all study records and source documentation.

624 *Study monitoring and audit*

625 The sponsor determined that as no individual participants were recruited to the
626 intervention, and it was not a clinical trial of an investigational medicinal product
627 (CTIMP) no formal monitoring and audit was required.

628

629 *Good Clinical Practice and Ethical Conduct*

630 The study will be conducted in accordance with the principles of the research
631 governance framework operational and good clinical practice in the relevant country.
632 A favorable ethical opinion has been obtained from the Scotland A REC (Reference
633 13/SS/0001) and local research and development approval has been obtained prior
634 to commencement of the study.

635 Local study investigator(s) will be appointed to each site (or for small units, groups of
636 sites). S/he will be responsible for the overall conduct of the study at the site and
637 compliance with the protocol and any protocol amendments.

638

639 **STUDY CONDUCT RESPONSIBILITIES**

640 *Protocol amendments*

641 Any changes in research activity, except those necessary to remove an apparent,
642 immediate hazard to the participant in the case of an urgent safety measure, will be
643 reviewed and approved by the Chief Investigator and Sponsor. Amendments to the
644 protocol will be submitted in writing to the appropriate REC and local Research and
645 Development (R&D) department for approval prior to participants being enrolled into
646 an amended protocol.

647 *Protocol violations and deviations*

Investigators will not implement any deviation from the protocol without agreement from the Chief Investigator and appropriate REC and R&D department approval except where necessary to eliminate an immediate hazard to trial participants. In the event that an Investigator needs to deviate from the protocol, the nature of and reasons for the deviation will be recorded. If this necessitates a subsequent protocol amendment, this will be submitted to the REC, and local R&D department for review and approval if appropriate.

Serious breach requirements

A serious breach is one which is likely to effect to a significant degree (a) the safety or physical or mental integrity of the participants of the trial; or b) the scientific value of the trial. If a potential serious breach is identified by the Chief investigator, Principal Investigator or delegates, the co-sponsors (accord.seriousbreach@ed.ac.uk) will be notified within 24 hours. It will be the responsibility of the co-sponsors to assess the impact of the breach on the scientific value of the trial, to determine whether the incident constitutes a serious breach and, if so, report it to the REC.

All violations will be assessed by the sponsor(s) to ascertain if they meet the criteria for a serious breach. If the sponsor(s) deem the incident to be a violation that does not constitute a serious breach from the protocol when identified, corrective and preventative actions will be taken where appropriate and they will be recorded in file notes, held within the TMF and ISF.

Study record retention

All study documentation will be kept for a minimum of 5 years from the protocol defined end of study point. When the minimum retention period has elapsed, study documentation will not be destroyed without permission from the sponsor.

674 *End of study*

675 The end of study date was finalised in the protocol after the study commenced; the
676 agreed end of study date is 31/12/2016. The Investigators and/or the trial steering
677 committee and/or the co-sponsor(s) have the right at any time to terminate the study
678 for clinical or administrative reasons.

679 The end of the study will be reported to the REC within 90 days, or 15 days if the
680 study is terminated prematurely. The Investigators will inform participants of the
681 premature study closure and ensure that the appropriate follow up is arranged for all
682 participants involved. A summary report of the study will be provided to the REC and
683 Regulatory Authority within 1 year of the end of the study.

684

685 **REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS**

686 Ownership of the data arising from this study resides with the study team. On
687 completion of the study, the study data will be analysed and tabulated, and a clinical
688 study report will be prepared in accordance with good clinical practice guidelines.
689 The clinical study report will be used as the basis for publication and presentation at
690 scientific meetings. Investigators have the right to publish orally or in writing the
691 results of the study. Summaries of results will also be made available to Investigators
692 for dissemination within their clinics (where appropriate and according to their
693 discretion).

694

695 **DISCUSSION**

696 The data provided by this study will inform the management of women with reduced
697 fetal movements; which has been recurrently identified by Confidential Enquiries into
698 antepartum stillbirths as suboptimal^{33 34}. This will provide much needed robust
699 evidence to determine whether increased maternal awareness of reduced fetal

700 movements combined with a standardised management protocol to identify acute or
701 chronic fetal compromise can reduce stillbirth ²⁷.

702

703 **PEER REVIEW**

704 This project has been peer reviewed internally, and was externally peer reviewed
705 during the process of securing funding from the Chief Scientist's Office of the
706 Scottish Government, Tommy's and Sands.

707

708 **FUNDING**

709 The AFFIRM study is investigator initiated and funded by Chief Scientist Office,
710 Scottish Government (CZH/4/882), Tommy's and Sands, the Stillbirth and Neonatal
711 Death Charity. CJW was supported in this work by NHS Lothian via the Edinburgh
712 Clinical Trials Unit. AEPH is supported by a Clinician Scientist fellowship from the
713 National Institute for Health Research (NIHR; CS-2013-009). This protocol presents
714 independent research funded by the National Institute for Health Research (NIHR).
715 The views expressed are those of the author(s) and not necessarily those of the
716 NHS, the NIHR or the Department of Health.

717

718 **ACKNOWLEDGEMENTS**

719 The authors would like to acknowledge the support of Perinatal Ireland and Dr Mary
720 Higgins (University College Dublin, National Maternity Hospital, Dublin).

721

722 **CONTRIBUTIONS**

723 Contributors AEPH, CJW, SJES, CJC, SCB, MRD, SW and JEN were involved in
724 developing the trial design. AEPH, CJW, SJES, AR and JEN were involved in
725 drafting and revision of the article. CJW and AR were involved in drafting the
726 statistical aspects of the protocol. JS provided feedback on behalf of a stakeholder

1
2
3 727 organisation. AEPH, CJW, SJES, CJC, SCB, JFF, MG, AH, FMM, EM, AR, MRD, JS,
4
5 728 SW and JEN were involved in preparing the overall study design. AEPH, JEN and
6
7 729 MRD prepared education videos for online training. AEPH, SJES, SJS, MG, AH,
8
9 730 FMM and JEN facilitated recruitment of sites. AEPH, CJW, SJES, CJC, SCB, JFF,
10
11 731 MG, AH, FMM, EM, AR, MRD, JS, SW and JEN will be involved in the collection,
12
13 732 management, analysis and interpretation of data and final writing of the trial report.
14
15 733
16
17 734 **COMPETING INTERESTS**
18
19 735 None declared.
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

736 **ABBREVIATIONS**

737	ACCORD	Academic and Clinical Central Office for Research & Development -
738		Joint office for University of Edinburgh and NHS Lothian
739	BMI	Body Mass Index
740	CTG	Cardiotocograph
741	CTIMP	Clinical Trial of an Investigational Medicinal Product
742	ECTU	Edinburgh Clinical Trials Unit
743	FGR	Fetal growth restriction
744	MHRA	Medicines and Healthcare products Regulatory Agency
745	NICE	National Institute for Health and Social Care Excellence
746	NIHR	National Institute for Health Research
747	NIMATS	Northern Ireland Maternity Statistics database
748	NRPS	National Perinatal Reporting System
749	ONS	Office of National Statistics
750	PSANZ	Perinatal Society of Australia and New Zealand
751	RCOG	Royal College of Obstetricians and Gynaecologists
752	R&D	Research and Development
753	REC	Research Ethics Committee
754	RFM	Reduced Fetal Movements
755	SPIMMR	Scottish Perinatal and Infant Mortality and Morbidity Report
756	TMF	Trial Master File
757	TSC	Trial Steering Committee
758	WHO	World Health Organisation

759
760

REFERENCES

1. Still-Birth Definition Act Great Britain Curr Law Statut Annot GB, 1992:1.
2. Flenady V, Wojcieszek AM, Middleton P, Ellwood D, Erwich JJ, Coory M, et al. Stillbirths: recall to action in high-income countries. *Lancet* 2016;387(10019):691-702.
3. Flenady V, Koopmans L, Middleton P, Froen JF, Smith GC, Gibbons K, et al. Major risk factors for stillbirth in high-income countries: a systematic review and meta-analysis. *Lancet* 2011;377(9774):1331-40.
4. Manktelow BM, Smith LK, Seaton SE, Hyman-Taylor P, Kurinczuk JJ, Field DJ, et al. Perinatal Mortality Surveillance Report - UK Perinatal Deaths for births from January to December 2014. Leicester:: The Infant Mortality and Morbidity Group, Department of Health Sciences, University of Leicester., 2016.
5. Lawn JE, Blencowe H, Pattinson R, Cousens S, Kumar R, Ibiebele I, et al. Stillbirths: Where? When? Why? How to make the data count? *Lancet* 2011;377(9775):1448-63.
6. Flenady V, Middleton P, Smith GC, Duke W, Erwich JJ, Khong TY, et al. Stillbirths: the way forward in high-income countries. *Lancet* 2011;377(9778):1703-17.
7. Heazell AE, Whitworth MK, Whitcombe J, Glover SW, Bevan C, Brewin J, et al. Research priorities for stillbirth: process overview and results from UK Stillbirth Priority Setting Partnership. *Ultrasound Obstet Gynecol* 2015;46(6):641-7.
8. Heazell AE, Froen JF. Methods of fetal movement counting and the detection of fetal compromise. *J Obstet Gynaecol* 2008;28(2):147-54.
9. Stacey T, Thompson JM, Mitchell EA, Ekeroma AJ, Zuccollo JM, McCowan LM. The Auckland Stillbirth study, a case-control study exploring modifiable risk factors for third trimester stillbirth: methods and rationale. *The Australian & New Zealand journal of obstetrics & gynaecology* 2011;51(1):3-8.

1
2
3 789 10. Warland J, O'Brien LM, Heazell AE, Mitchell EA. An international internet survey
4
5 790 of the experiences of 1,714 mothers with a late stillbirth: the STARS cohort
6
7 791 study. *BMC pregnancy and childbirth* 2015;15:172.
8
9 792 11. Warrander LK, Heazell AE. Identifying placental dysfunction in women with
10
11 793 reduced fetal movements can be used to predict patients at increased risk of
12
13 794 pregnancy complications. *Medical hypotheses* 2011;76(1):17-20.
14
15 795 12. Vintzileos AM, Fleming AD, Scorza WE, Wolf EJ, Balducci J, Campbell WA, et al.
16
17 796 Relationship between fetal biophysical activities and umbilical cord blood gas
18
19 797 values. *Am J Obstet Gynecol* 1991;165(3):707-13.
20
21 798 13. Warrander LK, Batra G, Bernatavicius G, Greenwood SL, Dutton P, Jones RL, et
22
23 799 al. Maternal perception of reduced fetal movements is associated with altered
24
25 800 placental structure and function. *PloS one* 2012;7(4):e34851.
26
27 801 14. Holm Tveit JV, Saastad E, Stray-Pedersen B, Bordahl PE, Froen JF. Maternal
28
29 802 characteristics and pregnancy outcomes in women presenting with decreased
30
31 803 fetal movements in late pregnancy. *Acta Obstet Gynecol Scand*
32
33 804 2009;88(12):1345-51.
34
35 805 15. Ptacek I, Sebire NJ, Man JA, Brownbill P, Heazell AE. Systematic review of
36
37 806 placental pathology reported in association with stillbirth. *Placenta*
38
39 807 2014;35(8):552-62.
40
41 808 16. Healthcare Improvement Scotland. Scottish Perinatal and Infant Mortality and
42
43 809 Morbidity Report 2010. Edinburgh: Healthcare Improvement Scotland, 2012.
44
45 810 17. Gardosi J, Kady SM, McGeown P, Francis A, Tonks A. Classification of stillbirth
46
47 811 by relevant condition at death (ReCoDe): population based cohort study. *BMJ*
48
49 812 (*Clinical research ed* 2005;331(7525):1113-7.
50
51 813 18. Saastad E, Winje BA, Stray Pedersen B, Froen JF. Fetal movement counting
52
53 814 improved identification of fetal growth restriction and perinatal outcomes--a
54
55 815 multi-centre, randomized, controlled trial. *PloS one* 2011;6(12):e28482.
56
57
58
59
60

- 1
2
3 816 19. Mangesi L, Hofmeyr GJ, Smith V, Smyth RM. Fetal movement counting for
4
5 817 assessment of fetal wellbeing. *Cochrane Database Syst Rev*
6
7 818 2015(10):CD004909.
8
9 819 20. Grant A, Elbourne D, Valentin L, Alexander S. Routine formal fetal movement
10
11 820 counting and risk of antepartum late death in normally formed singletons.
12
13 821 *Lancet* 1989;2(8659):345-9.
14
15 822 21. National Institute for Health and Clinical Excellence. Clinical Guideline 62 -
16
17 823 Antenatal care: routine care for the health pregnant woman. London: National
18
19 824 Institute for Health and Clinical Excellence, 2008.
20
21 825 22. Tveit JV, Saastad E, Stray-Pedersen B, Bordahl PE, Flenady V, Fretts R, et al.
22
23 826 Reduction of late stillbirth with the introduction of fetal movement information
24
25 827 and guidelines - a clinical quality improvement. *BMC pregnancy and childbirth*
26
27 828 2009;9:32.
28
29 829 23. Preston S, Mahomed K, Chadha Y, Flenady V, Gardener G, MacPhail J, et al.
30
31 830 Clinical practice guideline for the management of women who report
32
33 831 decreased fetal movements. Brisbane,: Australia and New Zealand Stillbirth
34
35 832 Alliance, 2010.
36
37 833 24. Royal College Of Obstetricians and Gynaecologists. Management of Reduced
38
39 834 Fetal Movements. London: RCOG, 2011.
40
41 835 25. Tveit JV, Saastad E, Stray-Pedersen B, Bordahl PE, Flenady V, Fretts R, et al.
42
43 836 Erratum to: Reduction of late stillbirth with the introduction of fetal movement
44
45 837 information and guidelines - a clinical quality improvement. *BMC pregnancy*
46
47 838 *and childbirth* 2010;10:49.
48
49 839 26. Froen JF, Heazell AE, Tveit JV, Saastad E, Fretts RC, Flenady V. Fetal
50
51 840 movement assessment. *Seminars in perinatology* 2008;32(4):243-6.
52
53 841 27. Hofmeyr GJ, Novikova N. Management of reported decreased fetal movements
54
55 842 for improving pregnancy outcomes. *Cochrane Database Syst Rev*
56
57 843 2012;4:CD009148.
58
59
60

28. Froen JF, Tveit JV, Saastad E, Bordahl PE, Stray-Pedersen B, Heazell AE, et al. Management of decreased fetal movements. *Seminars in perinatology* 2008;32(4):307-11.

29. Dutton PJ, Warrander LK, Roberts SA, Bernatavicius G, Byrd LM, Gaze D, et al. Predictors of poor perinatal outcome following maternal perception of reduced fetal movements--a prospective cohort study. *PloS one* 2012;7(7):e39784.

30. Royal College Of Obstetricians and Gynaecologists. The Investigation And Management Of The Small-For-Gestational-Age Fetus. London: RCOG, 2013.

31. Heazell AE, Green M, Wright C, Flenady V, Froen JF. Midwives' and obstetricians' knowledge and management of women presenting with decreased fetal movements. *Acta Obstet Gynecol Scand* 2008;87(3):331-9.

32. Jokhan S, Whitworth MK, Jones F, Saunders A, Heazell AE. Evaluation of the quality of guidelines for the management of reduced fetal movements in UK maternity units. *BMC pregnancy and childbirth* 2015;15:54.

33. Confidential Enquiry into Stillbirths and Deaths in Infancy. 8th Annual Report, 1 January–31 December 1999. London: Maternal and Child Health Research Consortium, 2001.

34. Draper ES, Kurinczuk JJ, Kenyon S, MBRRACE-UK. obo. MBRRACE-UK Perinatal Confidential Enquiry: Term, singleton, normally formed, antepartum stillbirth. Leicester: The Infant Mortality and Morbidty Studies, Department of Health Sciences, University of Leicester, 2015.

35. Saastad E, Winje BA, Israel P, Froen JF. Fetal movement counting--maternal concern and experiences: a multicenter, randomized, controlled trial. *Birth* 2012;39(1):10-20.

36. Saastad E, Israel P, Ahlborg T, Gunnes N, Froen JF. Fetal movement counting--effects on maternal-fetal attachment: a multicenter randomized controlled trial. *Birth* 2011;38(4):282-93.

- 1
2
3 872 37. Hussey MA, Hughes JP. Design and analysis of stepped wedge cluster
4
5 873 randomized trials. *Contemp Clin Trials* 2007;28(2):182-91.
6
7 874 38. ESRI Health Research and Information Division. Perinatal Statistics Report 2009,
8
9 875 2011.
10
11 876 39. Tominey E. Maternal smoking during pregnancy and early child outcomes.
12
13 877 Discussion Paper no. 828. London: Centre for Economic Performance,
14
15 878 London School of Economics., 2007.
16
17 879
18
19 880
20
21
22 881
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

FIGURE LEGENDS

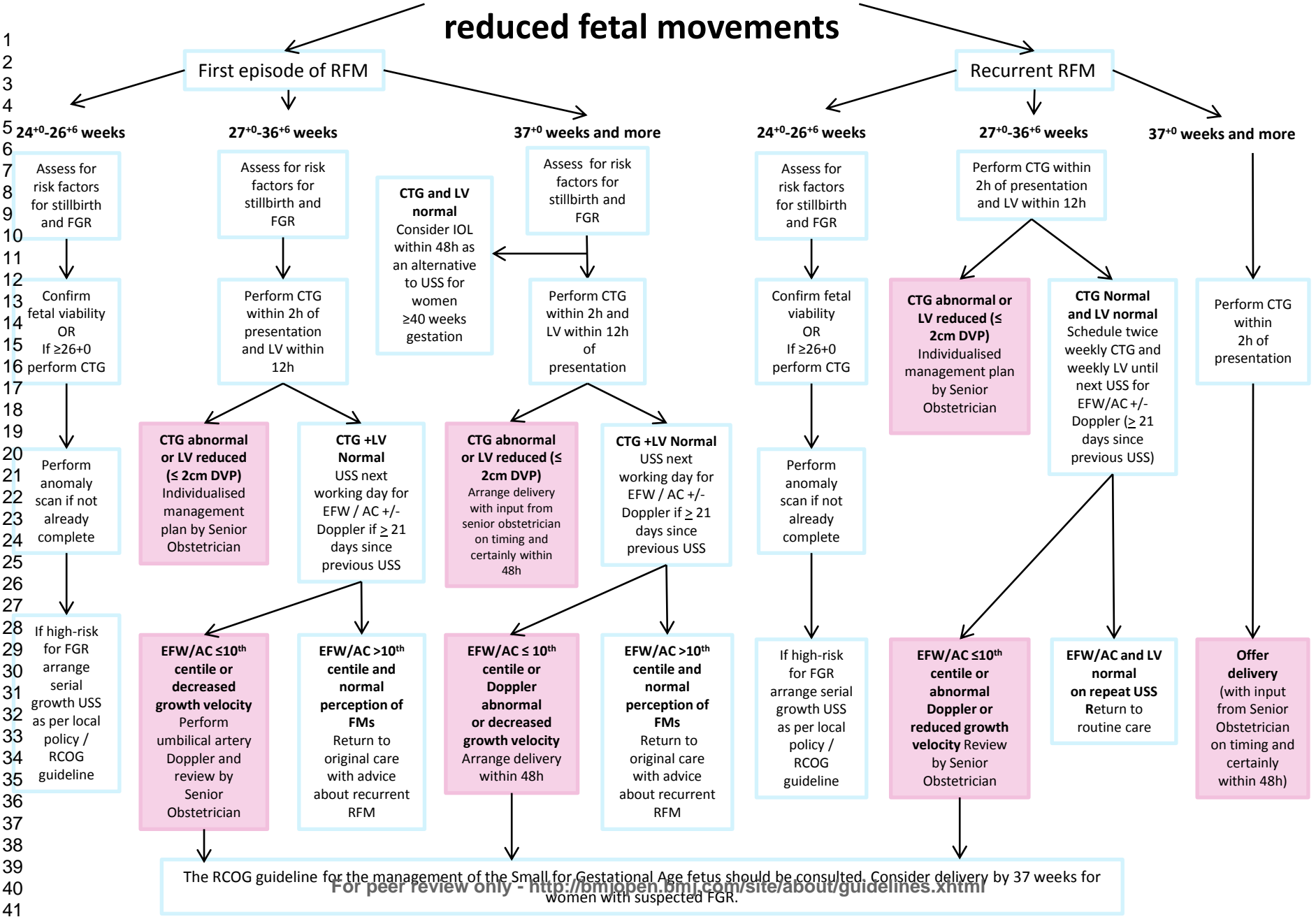
Figure 1 - Stepped wedge design. The shaded areas indicate periods in which the interventions are being implemented. The order in which hospital groupings implement the interventions will be determined via randomization.

Figure 2 – Flow chart for the management of women presenting with reduced fetal movements for sites implementing the AFFIRM study. Abbreviations: AC - abdominal circumference, CTG- cardiotocograph, DVP - deepest vertical pool, EFW - estimated fetal weight, FGR - fetal growth restriction, LV - liquor volume, RFM - reduced fetal movement, USS - ultrasound scan.

Hospital groupings	Months since Start of Trial								
	1-4	5-8	9-12	13-16	17-20	21-24	25-28	29-32	33-36
1-3									
4-6									
7-9									
10-12									
13-15									
16-18									
19-21									
22-24									

Woman attends with reduced fetal movements

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43



The RCOG guideline for the management of the Small for Gestational Age fetus should be consulted. Consider delivery by 37 weeks for women with suspected FGR.



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	____ Page 1 ____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	____ Page 4 ____
	2b	All items from the World Health Organization Trial Registration Data Set	_Included throughout protocol_
Protocol version	3	Date and version identifier	____ Page 4 ____
Funding	4	Sources and types of financial, material, and other support	____ Page 28 ____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	_Names and affiliations Page 1 and 2; Contributions Page 28_
	5b	Name and contact information for the trial sponsor	____ Page 24 ____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	_Not applicable_

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	___Page 24___
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	__Pages 5-11__
	6b	Explanation for choice of comparators	__Pages 8-9__
Objectives	7	Specific objectives or hypotheses	__Pages 11-12__
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	__Pages 13- 14 and Figure 1 ___
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	__Pages 13 & 16__
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	__Pages 14-15__
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	__Pages 17-18 and Figure 2__
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	__Not applicable in AFFIRM trial__
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	__Pages 17-18__
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	__Not applicable__

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	__Pages 12-13__
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	__Randomisation by site explained in Figure 1 and Pages 13-14__
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	__Pages 21-22__
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	__Page 22__
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	__Page 17__
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	__Page 17__
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	__Page 17__
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	__Page 17__
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	__Not applicable in AFFIRM study__

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	__Pages 18-21__
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	__Not applicable__
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	__Pages 19-20__
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	__Pages 22-23__
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	__Page 23__
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	__Pages 22-23__

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	_DMC not required, explanation Pg 24__
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	__Pages 18, 25-26__
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	__Page 24__
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	__Page 13__

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	__Page 25__
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	__Page 25__
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	__Page 25__
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	__Not applicable__
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	__Page 20__
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	__Page 29__
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	__Page 27__
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	__Page 24__
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	__Page 27__
	31b	Authorship eligibility guidelines and any intended use of professional writers	__Page 28__
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	__Not applicable__

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_Not Applicable__
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_Not Applicable__

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](#)" license.

WHO TO CONTACT IF YOU ARE CONCERNED: (space for sticky with local contact information)



APS Group Scotland
DPPAS33137
Version 3 March 2015



In touch with YOUR BABY

A guide to your baby's
movements during
pregnancy



For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>

Why are my baby's movements important?

Why are we asking women to get to know their baby's movements?

One of the easiest ways to tell if your baby is healthy is to be aware of how much he or she is moving. Every baby is different and we are asking women to take time to become familiar with their baby's own individual pattern of movements. A reduction or change in **your** baby's movements is what is important.

What can affect my baby's movements?

You are less likely to be aware of your baby's movements when active or busy. Some drugs e.g. strong pain relief or sedatives can get into an unborn baby's circulation and affect the movements. Alcohol and smoking (active and passive smoking) may also affect the baby.

Why are my baby's movements important?

If you notice your baby is moving less than usual, or the pattern of movements has changed, this could be the first sign that your baby may not be well or is not growing properly in the womb. Research has shown that a reduction in the baby's movements may indicate an increased risk of stillbirth. You may hear your midwife or doctor referring to 'reduced fetal movement', or RFM for short.

What are the risks of stillbirth?

Stillbirth affects one in 200 babies after 24 weeks gestation and is one of the most common of the serious complications of pregnancy, affecting the lives of around 4,000 families every year in the UK.

One of the easiest ways to tell if your baby is healthy is to see how much he or she is moving. This booklet tells you what to look out for during your pregnancy.

Every baby is different. It is good to get to know your baby's own movements and the pattern of their sleeping and waking and report to us if you notice a reduction in these movements.



Try to get to know the times of the day when you are most likely to feel your baby move.



18-24 WEEKS



24-36 WEEKS



Most women begin to feel their baby move between 18-24 weeks. At first it may feel like 'bubbles', 'flutterings' or 'like trapped wind'. These are often very short and stop and start. It might take you a little while to be sure what you are feeling. But you will soon get to know the feelings. If this is your second baby, you will know what to look out for and may recognise your baby moving sooner.

Everyone is different when it comes to their movements. There are many reasons you might not feel movements as early as you expect. This includes your body weight, the position of your baby and the location of your placenta. What is important is your baby is growing well. Your midwife will be able to discuss this with you further at your 22 week check.

You will have your own way of describing your baby's own movements. Women often describe their baby's movements as 'rolling', 'kicking', 'pushing', 'jabs', 'elbowing' and 'stretches'.

Between 24-36 weeks you will start to recognise your baby's movements more quickly and become more used to the feeling. It is usually easier to feel your baby's movements when you are lying down, e.g. at night time. It is harder to feel your baby move when you are on your feet and moving around.

Try to get to know the times of the day you are most likely to feel your baby move. This will help you to know if he or she is moving less than normal or if movements have stopped.

Occasionally your baby will get hiccups. These do not count as movements. If you are unsure what you should expect when your baby hiccups, speak to your midwife.



BMJ Open

Can Promoting Awareness of Fetal movements and Focussing Interventions Reduce Fetal Mortality? - A stepped wedge cluster randomised trial (AFFIRM)

Journal:	BMJ Open
Manuscript ID	bmjopen-2016-014813.R1
Article Type:	Protocol
Date Submitted by the Author:	10-Jan-2017
Complete List of Authors:	<p>Heazell, Alexander; University of Manchester, Maternal and Fetal Health Research Centre</p> <p>Weir, Christopher; University of Edinburgh, MRC Hub for Trials Methodology Research; Edinburgh Clinical Trials Unit</p> <p>Stock, Sarah; Queen's Medical Research Institute, EH16 4TJ, Tommy's Centre for Maternal and Fetal Health, MRC Centre for Reproductive Health,; School of Women's and Infants' Health, University of Western Australia, Crawley WA 6009. (FMM)</p> <p>Calderwood, Catherine; The Scottish Government St Andrew's House, EH1 3DG., Chief Medical Officer for Scotland,</p> <p>CunninghamBurley, Sarah; University of Edinburgh, Public Health Sciences</p> <p>Froen, Frederik; Nasjonalt folkehelseinstitutt, Division of Epidemiology</p> <p>Geary, Michael; Rotunda Hospital, Parnell Square</p> <p>Hunter, Alyson; Royal Maternity Hospital, Grosvenor Road, BT12 6BB</p> <p>McAuliffe, Fionnuala; University College Dublin,</p> <p>Murdoch, Edile; Royal Infirmary of Edinburgh, NHS Lothian, EH16 4SA., Department of Neonatology</p> <p>Rodriguez, Aryelly; University of Edinburgh, (ECTU) Edinburgh Clinical Trials Unit</p> <p>Ross-Davie, Mary; NHS Education for Scotland, 3rd Floor, Hanover Buildings, 66 Rose Street, EH2 2NN.</p> <p>Scott, Janet; Sands, Victoria Charity Centre, Suite GF2 Ground Floor, 11 Belgrave Road, SW1V 1RB.</p> <p>Whyte, Sonia; Queen's Medical Research Institute, EH16 4TJ, Tommy's Centre for Maternal and Fetal Health, MRC Centre for Reproductive Health,</p> <p>Norman, Jane; , Queen's Medical Research Institute, EH16 4TJ</p>
Primary Subject Heading:	Obstetrics and gynaecology
Secondary Subject Heading:	Research methods
Keywords:	Reduced Fetal Movements, Perinatal Mortality, Stillbirth, Neonatal Death, Fetal Growth Restriction

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

1 Study Protocol

2 Can Promoting Awareness of Fetal movements and Focussing Interventions Reduce
3 Fetal Mortality? - A stepped wedge cluster randomised trial (AFFIRM)

4 Alexander E P HEAZELL,^{1,2} alexander.heazell@manchester.ac.uk

5 Christopher J WEIR,^{3,4} christopher.weir@ed.ac.uk

6 Sarah J E STOCK,^{5,6} sarah.stock@ed.ac.uk

7 Catherine J CALDERWOOD,⁷ catherine.calderwood@scotland.gsi.gov.uk

8 Sarah CUNNINGHAM-BURLEY,⁴ sarah.c.burley@ed.ac.uk

9 J Frederik FROEN,⁸ frederik.froen@fhi.no

10 Michael GEARY,⁹ mppgeary@gmail.com

11 Alyson HUNTER,¹⁰ alyson.hunter@belfasttrust.hscni.net

12 Fionnuala M MCAULIFFE,¹¹ fionnuala.mcauliffe@ucd.ie

13 Edile MURDOCH,¹² edile.murdoch@nhslothian.scot.nhs.uk

14 Aryelly RODRIGUEZ,^{3,4} aryelly.rodriguez@ed.ac.uk

15 Mary ROSS-DAVIE,¹³ mary.ross-davie@nes.scot.nhs.uk

16 Janet SCOTT¹⁴ janet.scott@uk-sands.org

17 Sonia WHYTE⁵ sonia.whyte@ed.ac.uk

18 Jane E NORMAN.⁵ jane.norman@ed.ac.uk

19

20 1. Maternal and Fetal Health Research Centre, Institute of Human Development,
21 University of Manchester. 2. St. Mary's Hospital, Central Manchester University
22 Hospitals NHS Foundation Trust, Manchester Academic Health Science Centre,
23 Manchester, M13 9WL. 3. Edinburgh Clinical Trials Unit, Edinburgh, UK 4. Centre for

24 Population Health Sciences, Usher Institute of Population Health Sciences and
25 Informatics, University of Edinburgh, Teviot Place, Edinburgh EH8 9AG. 5. Tommy's
26 Centre for Maternal and Fetal Health, MRC Centre for Reproductive Health, Queen's
27 Medical Research Institute, Edinburgh, EH16 4TJ.6. School of Women's and Infants'
28 Health, University of Western Australia, Crawley WA 6009. (FMM) 7. Chief Medical
29 Officer for Scotland, The Scottish Government St Andrew's House Edinburgh EH1
30 3DG. 8. Department of International Public Health, Norwegian Institute of Public
31 Health, PB 4404 Nydalen, N-0403 Oslo, Norway, 9. Rotunda Hospital, Parnell
32 Square, Dublin 1, Ireland. 10. Centre for Fetal Medicine, Royal Maternity Hospital,
33 Grosvenor Road, Belfast, BT12 6BB 11. UCD Obstetrics & Gynaecology, School of
34 Medicine, University College Dublin, Ireland. National Maternity Hospital, Dublin,
35 Ireland. 12. Department of Neonatology, Royal Infirmary of Edinburgh, NHS Lothian,
36 Edinburgh, EH16 4SA. 13. NHS Education for Scotland, 3rd Floor, Hanover
37 Buildings, 66 Rose Street, Edinburgh EH2 2NN. 14. Sands, Victoria Charity Centre,
38 Suite GF2 Ground Floor, 11 Belgrave Road, London, SW1V 1RB.

39

Abstract

Background - In 2013, the stillbirth rate in the UK was 4.2 per 1,000 live births, ranking 24th out of 49 high-income countries, with an annual rate of reduction of only 1.4% per year. The majority of stillbirths occur in normally formed infants, with (retrospective) evidence of placental insufficiency the commonest clinical finding. Maternal perception of reduced fetal movements (RFM) is associated with placental insufficiency and increased risk of subsequent stillbirth.

This study will test the hypothesis that the introduction of a package of care to increase women's awareness of the need for prompt reporting of RFM and standardised management to identify fetal compromise with timely delivery in confirmed cases, will reduce the rate of stillbirth. Following the introduction of a similar intervention in Norway the odds of stillbirth fell by 30%, but the efficacy of this intervention (and possible adverse effects and implications for service delivery) have not been tested in a randomised trial.

Methods - We describe a stepped wedge cluster trial design, in which participating hospitals in the UK and Ireland will be randomized to the timing of introduction of the care package. Outcomes (including the primary outcome of stillbirth) will be derived from detailed routinely collected maternity data, allowing us to robustly test our hypothesis. The degree of implementation of the intervention will be assessed in each site. A nested qualitative study will examine the acceptability of the intervention to women and health care providers and identify process issues including barriers to implementation.

Discussion - The data provided by this study will inform the management of women with RFM; which has been recurrently identified as suboptimal in cases of stillbirth. This will provide robust evidence to determine whether increased maternal awareness of RFM combined with a standardised management protocol to identify acute or chronic fetal compromise can reduce stillbirth.

67 *Trial Registration*

68 www.clinicaltrials.gov NCT01777022

69 *Version*

70 Protocol Version 4.2, 19th December 2016

71 *Keywords*

72 Reduced Fetal Movements; Perinatal Mortality; Stillbirth; Neonatal Death; Fetal
73 Growth Restriction.

74

75 **STRENGTHS AND LIMITATIONS OF THIS STUDY**

- 76 • This trial directly addresses the need for studies of the information given to
77 women regarding fetal movements and the subsequent management of reduced
78 fetal movements identified by Confidential Enquiries into Antepartum Stillbirths,
79 Systematic Reviews and the Stillbirth Priority Setting Partnership.
- 80 • A stepped-wedge cluster trial design in combination with routinely collected
81 maternity data allows the trial to be adequately powered to detect a difference in
82 stillbirth as a primary outcome.
- 83 • The pragmatic nature of the study represents the potential impact of the
84 introduction of such standardised care into clinical practice.
- 85 • The nested qualitative study will provide information regarding the acceptability
86 of the intervention and identify barriers and facilitators to its adoption.
- 87 • The lack of information on resource use before and throughout the study period
88 limits the ability to understand the consequences of the intervention on maternity
89 unit workload.

90

91

92 INTRODUCTION

93 *Stillbirth*

94 Stillbirth, defined in the UK as a baby with no signs of life after 24 weeks of completed
95 pregnancy ¹, remains the major cause of perinatal mortality in high-income
96 environments, with a recent series of papers in the Lancet on stillbirth issue calling for
97 renewed action in this area ². There is no single “cause” of stillbirth, and a significant
98 proportion of stillbirths remain unexplained, but fetal growth restriction, maternal
99 hypertension and low socioeconomic status are amongst the identifiable risk factors ³.
100 The concept that more can be done to reduce stillbirth in the UK and Ireland is
101 supported by data showing a marked variation in rates between resource rich
102 countries, when similar definitions of stillbirth are used ². Notably, the UK has a higher
103 rate than comparable resource rich countries such as Germany, Netherlands, New
104 Zealand and Norway with rates in the UK some 50% greater than those of the
105 Netherlands. Disappointingly, the annual rate of reduction in stillbirth from 2000 to
106 2014 in the UK was only 1.4% compared to 6.8% in the Netherlands and 2.8% in New
107 Zealand ². Rates of stillbirth in Scotland (3.7 per 1,000 births in 2014) and Ireland, at
108 (4.4 per 1,000 livebirths in 2013) are similar to rates in England and Wales at 4.2 per
109 1,000 livebirths (England and Wales, 2014) ⁴. The reduction of avoidable harm for
110 women and babies is viewed as a major priority for Government and its agencies
111 throughout the UK and Ireland. Consequently, several initiatives have been
112 developed by national governments in the UK and Ireland including the Scottish
113 Government Stillbirth Working Group, NHS England Saving Babies’ Lives Care
114 Bundle and the Welsh Assembly 1000 Lives Plus strategy. These strategies have
115 identified the need for better evidence to guide efforts to prevent stillbirths.
116 Using a robust priority setting strategy ⁵ the Lancet Stillbirth’s series steering
117 committee identified issues around detection and management of reduced fetal
118 movements (RFM) amongst the top ten key research questions on prevention and

management of stillbirth ⁶. This was confirmed in the UK-based Stillbirth Priority Setting partnership involving over 1,700 parents and professionals which identified two relevant issues among the highest ranked research questions regarding stillbirth: i) which investigations identify a fetus at risk of stillbirth after a mother believes she has experienced reduced fetal movements? and ii) would more accessible evidence-based information on signs and symptoms of stillbirth risk, designed to empower women to raise concerns with healthcare professionals, reduce the incidence of stillbirth? ⁷ Thus, RFM has been identified as a highly-relevant area of study by parents, professionals and researchers.

Reduced Fetal Movements, Stillbirth and Placental Insufficiency

There is a clear association between maternal perception of RFM and late stillbirth dating back over four decades ⁸. In a recent series of 2,000 women, the adjusted OR (95% CI) of late stillbirth in women with RFM (compared with controls) was 2.37 (1.29-4.35) ⁹. One international study of 1,714 women who experienced a stillbirth found that 30% had noted significant RFM prior to the diagnosis of stillbirth ¹⁰. Although the mechanisms have not been fully delineated, it is likely that RFM and stillbirth are linked by a common pathology, that of placental dysfunction ¹¹. There is good evidence linking placental dysfunction and RFM. Compared to controls with an active fetus women who have fewer fetal movements on ultrasound scan immediately prior to caesarean section are more likely to have umbilical cord gas measurements indicative of acidaemia, hypoxaemia, and hypercapnia ¹². Women delivering within one week of an episode of RFM show differences in placental structure and function which are reminiscent of those seen in fetal growth restriction (FGR) and stillbirth ^{13 14}. Additionally, the odds of fetal growth restriction (FGR, defined as being at less than the 10th centile for gestation adjusted birthweight) were greater in women with RFM compared with controls (adjusted OR 1.6, 95% CI 1.1–2.2 ¹⁵). Taken together these

data are strong evidence that placental dysfunction is associated with RFM, and a causative pathway seems likely.

The evidence linking placental dysfunction and stillbirth is even stronger; a systematic review of placental pathology in stillbirths described abnormalities in up to 65% of cases¹⁶. Amongst the 291 stillbirths in Scotland in 2010, 137 (47%) had evidence of placental dysfunction¹⁷. Given that the placenta was examined in only 80% of stillbirths, the true prevalence of placental dysfunction is likely to be higher. In addition, between 20%-40% of stillborn babies are reported to have FGR, as defined by a birthweight less than the 10th centile¹⁸. Additionally, the Lancet report notes that “placental pathologies accounted for one in four deaths across all gestational ages, and were contributory or causal in more than half of cases”⁶. Given that stillbirth is strongly related to placental dysfunction, and RFM is a “biomarker” of placental dysfunction then better management of women presenting with RFM focussing on the detection of placental dysfunction might reduce the risk of stillbirth.

Formal Fetal Movement Counting

Although prenatal detection of FGR is improved by fetal movement counting¹⁹, a systematic review²⁰, and a large and influential cluster randomised trial (which dominates the systematic review) showed that routine fetal movement counting using the count to ten charts had no effect on perinatal mortality²¹. Thus, the National Institute for Health and Social Care Excellence (NICE) recommended that “Routine formal fetal movement counting should not be offered”²². Importantly, the large cluster randomised trial tested a specific alarm limit for RFM, but did not recommend a specific management strategy for women who did present with RFM. There were two important observations from this study, firstly that in both groups the perinatal mortality rate was lower than contemporary or subsequent periods in the UK and secondly that more women in the fetal movement counting arm came in with a live baby who subsequently died compared with the control arm (19 vs 11), suggesting

174 that one reason the strategy failed to reduce perinatal mortality was inadequate
175 investigation and management of those presenting with RFM ²¹.

176
177 *Optimal strategy for determining RFM to prompt maternal presentation to the*
178 *maternity service*

179 Maternal concern about RFM is a common reason to contact maternity services with
180 between 6-15% of women presenting during the third trimester.^{23 24} Nevertheless,
181 delays in reporting RFM to maternity care providers may increase the risk of adverse
182 outcome.^{25 26} The lack of good-quality information given to women about fetal
183 movements has been highlighted as an example of suboptimal care in Confidential
184 Enquiries into Antepartum Stillbirth.^{27 28} Qualitative studies suggest that women
185 frequently perceive RFM two days prior to the diagnosis of fetal death, and in some
186 cases contractions were misinterpreted as fetal movements.²⁹ Therefore, giving
187 information to women regarding fetal movements and when they should be
188 concerned about RFM is a key component of an intervention to reduce stillbirth.

189 However, giving clear information about RFM can be challenging as there is no
190 uniform threshold of fetal movements below which perinatal morbidity increases ²⁴,
191 and no evidence that a specific threshold performs better than maternal perception of
192 reduced fetal movements alone ⁸. Current guidelines from the RCOG and PSANZ ³⁰
193 ³¹, informed by a large Norwegian study ³² suggest that it is maternal *perception* of
194 decreased fetal movement which is important. Therefore, information for pregnant
195 women in this study (shown in Supplementary File 1) described the importance of
196 fetal movements, the need to get to know normal fetal activity, how fetal movements
197 change in late pregnancy and who to contact if the mother perceives RFM. The
198 educational package aimed to ensure that these messages were reinforced by staff
199 behaviour at antenatal contacts.

200
201 *Optimal strategy for investigation and management of women presenting with RFM.*

1
2
3 202 A recent systematic review found there are no proven strategies for the investigation
4
5 203 and management of women presenting with RFM ³³. Cardiotocography (CTG) is
6
7 204 routinely used to ascertain fetal wellbeing, and it is the cornerstone of the RCOG
8
9 205 guideline ³¹. However, data from Norway, suggests that ultrasound assessment of
10
11 206 fetal size is often the most helpful investigation, performing well on both an absolute
12
13 207 basis, and compared with other interventions ³⁴. In a series of over 3,000 women with
14
15 208 RFM, ultrasound (including measurement of fetal biometry and liquor volume) was
16
17 209 found to be useful in detecting abnormalities in 11.6% of scans. In 71% of women in
18
19 210 whom an abnormality was found, ultrasound was the only technique that detected an
20
21 211 abnormality. Additionally, 85% of abnormalities detected by ultrasound, were
22
23 212 important in informing the clinical management of the woman ³⁴. These data are
24
25 213 supported by a smaller UK study which found that abnormalities detected on CTG or
26
27 214 ultrasound scan were most strongly associated with adverse outcome in women with
28
29 215 RFM, with identification of abnormal estimated fetal growth centile on scan being the
30
31 216 test most highly predictive of poor outcome ³⁵. Perhaps this is not surprising, given the
32
33 217 strong association between RFM and placental dysfunction and the central
34
35 218 importance of ultrasound in the identification and management of small for gestational
36
37 219 age babies ³⁶. Given these data, it is concerning that a survey of clinicians in Scotland
38
39 220 showed that fewer than 5% would routinely refer women with RFM for ultrasound
40
41 221 examination (unpublished data from June 2012), and a survey of 223 UK midwives
42
43 222 and obstetricians described that 17.9% of respondents would perform an ultrasound
44
45 223 scan ³⁷. These views of clinicians may reflect the variable quality of local guidelines,
46
47 224 which are frequently not based on national recommendations, even those for which
48
49 225 there is strong evidence ³⁸. The variation in information given to women and
50
51 226 subsequent management of RFM has been highlighted as sources of suboptimal care
52
53 227 in two confidential enquiries into antepartum stillbirth ^{27 28}. Therefore, we believe that
54
55 228 current investigation of women presenting with RFM is inadequate, hence using the
56
57 229 best available evidence, we have drafted what we consider to be a robust evaluation
58
59
60

230 protocol for investigation of women with RFM.

231 *Potentially efficacy of a package of intervention for RFM*

232 Supportive data for the package of interventions used in this study (information for

233 women and standardised management protocol) comes from a large observational

234 “clinical quality improvement study” in Norway which found a significant fall in rates of

235 stillbirth (from 3.0/1,000 to 2.0/1,000 [OR 0.67 95% CI 0.48–0.93]) after the

236 introduction of an intervention package consisting of written information for women

237 about awareness of RFM combined with consensus guidelines for health

238 professionals about their management ³². Although this study was not randomised,

239 and therefore constitutes only level II-3 evidence, it has informed recommendations

240 from the Royal College of Obstetricians and Gynaecologists (RCOG) and Perinatal

241 Society of Australia and New Zealand (PSANZ) that “women should be advised to be

242 aware of their baby’s individual pattern of movements and that if they are concerned

243 about a reduction in or cessation of fetal movementsthey should contact their

244 maternity unit” ^{30 31}. Following initial publication of the Norwegian study, a re-analysis

245 was required as discrepancies between stillbirth rates in the study and the Medical

246 Birth Registry of Norway were identified. This reanalysis found the reduction in

247 stillbirth rates was of borderline statistical significance (OR 0.72, 95% CI 0.50-1.03).

248 The authors concluded that further studies were needed to determine whether this

249 approach was associated with a reduction in stillbirth ³⁹.

250 Importantly, in the Norwegian study, there was no increase in the proportion of

251 women who presented with RFM when rates were compared before and after the

252 intervention ³². However, women with RFM presented significantly earlier to hospital

253 than they had hitherto, potentially allowing time for intervention to reduce perinatal

254 mortality. These data suggest that a package of interventions encouraging women

255 with RFM to present early to hospital, combined with a structured approach to their

256 management might reduce rates of stillbirth without contributing to a large increase in

257 admissions antenatally.

258

259 *Potential harms of a package of care around increased awareness and optimised*
260 *management of RFM*

261 Any clinical intervention which aims to improve outcomes also has the ability to do
262 harm. Thus, it is essential that the intervention proposed is rigorously evaluated using
263 the gold standard technique of a randomised trial, rather than being introduced as a
264 service development. When the study began, there was a small window of
265 opportunity to do this, as the enthusiasm to improve current management of RFM is
266 such that routine introduction of the package of care is unlikely to be delayed much
267 further than the current scheduled end date of this study. Possible harms of a
268 package of care consisting of a management plan for identification and delivery of the
269 “at risk” fetus, together with strategies for increasing pregnant women’s awareness of
270 the need to report early include increased maternal anxiety and increased
271 intervention (including hospital admission, induction of labour and Caesarean section)
272 which itself is associated with pregnancy related complications. The available
273 evidence is reassuring on some of these issues. A systematic review of 23
274 publications from 16 studies found three studies involving 2,030 women addressing
275 maternal concern and an additional three studies involving 1,468 women investigating
276 maternal-fetal attachment. These demonstrated no evidence of increased maternal
277 anxiety and results regarding maternal-fetal attachment were discordant.⁴⁰ In the
278 Norwegian service development study, the package of care increased rates of follow
279 up of women, but there was no increase in admissions overall, admissions for
280 induction or admissions for emergency caesarean section ³² – again, whilst
281 reassuring these outcomes require formal evaluation in a randomised and relevant
282 setting to the UK and Republic of Ireland. The final possible harm of the package is
283 around increased resource use, and the opportunity cost of focussing on RFM rather
284 than other potential methods to prevent stillbirth.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

285

286

287

288

289

290

291

292

293

294

295

296

297

298

299

300

301

302

303

304

305

306

307

308

309

RATIONALE

The aim of this study is to test the hypothesis that a package of interventions consisting of strategies for increasing pregnant women’s awareness of the need to report early when they perceive a reduction in fetal movements, followed with a management plan for identification and delivery of the “at risk” fetus in such women, will reduce rates of stillbirth.

STUDY OBJECTIVES

Primary Objective

The primary objective is to answer the research question ‘Does the introduction of a protocol for detection and management of decreased fetal movements reduce rates of stillbirth?’ The secondary objectives are to answer the following research questions:

- What is the effect of the intervention on rates of caesarean section and induction of labour?
- What is the effect of the intervention on rates of admission to the neonatal intensive care unit?
- What is the effect of the intervention on the proportion of women with FGR remaining undelivered by 40 weeks gestation?
- What is the acceptability of such a package of care to pregnant women and their health care providers?
- What other process outcomes are influenced by the intervention, such as health care provider/patient interactions?

ENDPOINTS

Primary Outcome

The primary endpoint is stillbirth (antepartum and intrapartum). We will use the UK definition of stillbirth which is “a baby delivered without signs of life after 23⁺⁶ weeks”⁴. Where gestation is uncertain we will include all babies with a birth weight of 500g or more.

Secondary Endpoints

Other measures of perinatal mortality including:

- Stillbirth at 37 weeks gestation and above
- Stillbirth at 28 weeks gestation and above (WHO definition of stillbirth)
- Stillbirth at 22 weeks gestation and above (international stillbirth alliance definition)
- Stillbirths amongst normally formed infants of 22 weeks gestation and above, 24 weeks gestation and above, 28 weeks gestation and above and 37 weeks gestation and above.
- Perinatal mortality (defined as stillbirth at 24 weeks gestation and above and deaths in the first seven days of life)
- Rates of caesarean section
- Rates of induction of labour (for any indication)
- Rates of elective delivery (induction of labour and caesarean section prior to the onset of labour) overall
- Rates of induction of labour at 39 weeks gestation or later
- Mean gestation at induction of labour
- Rates of admission to the neonatal unit (and their reasons)

- 334 • Rates of admission to the neonatal unit for more than 48 hours
- 335 • Rates of admission to the neonatal unit for term babies (those born at 37
- 336 weeks 0 days or greater)
- 337 • Proportion of infants with fetal growth restriction (less than the 5th centile,
- 338 customised for gender) remaining undelivered at or after 40 weeks gestation
- 339 • Birthweight centile (according to the Intergrowth birthweight centile calculator
- 340 at <https://intergrowth21.tghn.org>)
- 341 • Rates of spontaneous vaginal delivery
- 342 Other secondary outcomes are the baby parameters:
- 343 • Gestation at birth
- 344 • Proportion of babies born preterm (<37 weeks gestation)
- 345 • Gender of the baby
- 346 • Birthweight of the baby
- 347 • Apgar score at 5 minutes
- 348 • Proportion of babies with 5 minute Apgar score < 7
- 349 • Proportion of babies with 5 minute Apgar score < 4
- 350 • Resuscitation required at birth

351 We will also collect the following data: maternal age, maternity unit of delivery,
352 birthweight, gestation of delivery, parity, gestation, sex, smoking (current and ever),
353 maternal body mass index (BMI), number of babies (one or more), ethnicity (to allow
354 a customised birthweight centile to be generated), method of delivery, deprivation
355 category (where available) and other neonatal variables including Apgar score and
356 encephalopathy. Adjustment will be made for the following variables: (maternal age,

maternity unit of delivery, parity, smoking status, maternal BMI, number of babies
[one or more] and ethnicity)

359

360 STUDY DESIGN

361 This is a multicentre, stepped wedge cluster randomised trial of a package of care
362 consisting of a management plan for identification and delivery of the 'at risk' fetus,
363 together with strategies for increasing pregnant women's awareness of the need to
364 report RFM early. The trial developed from a planned quality improvement project
365 proposed by the Scottish Government to reduce stillbirths. This was planned to
366 emphasise the importance of fetal movement monitoring and was to be rolled out to
367 all NHS maternity units in Scotland. However, prior to this change it was agreed that
368 the roll out could be performed in such a way as to allow the assessment of the effect
369 of the intervention, the stepped-wedge design would be the natural choice in this
370 circumstance.

371 The study will take place in participating hospitals in the UK and Ireland (a complete
372 list is available <http://www.crh.ed.ac.uk/affirm/randomised-hospitals/>). A nested
373 qualitative study will examine the acceptability of the intervention to patients and
374 health care providers and identify process issues (barriers to implementation).
375 Clinical audit (detailed in supplementary information 2) conducted after the change in
376 practice will be used to determine the effect of interventions on process outcomes
377 (e.g. number of women presenting with reduced fetal movements, interval between
378 perceiving reduced fetal movements and presentation to hospital, number of
379 ultrasound scans, number of admissions for induction of labour). A diagram indicating
380 randomisation of hospital groupings in the stepped wedge design is shown in Figure
381 1.

382 The interventions will be introduced over a 32 month period. Data will be collected
383 over a 36 month period. Data in the ‘active phase’ after introduction of the
384 intervention will be compared to data in the ‘control phase’ – the period during which
385 usual care processes in study sites are followed from study start to the time of
386 introduction of the intervention. Given that it will take individual units some time (a) to
387 effect change in management in their unit from time of introduction of the intervention
388 and (b) that it will take some time for this change in practice to impact on clinical
389 outcomes, we plan a “washout” period of two months after the introduction of the
390 intervention during which data will not be included in either group for analysis (Figure
391 1). Data will be collected four months after the last birth, a further two months has
392 been included for data analysis, giving a total study duration of 42 months.

393

394 **STUDY POPULATION**

395 *Number of participants*

396 Participants will be those delivering at all the sites over the study period (36 months).
397 All eligible women will be recruited to the cluster randomised controlled trial. Based
398 on previous delivery numbers, after accounting for a washout period of two months
399 (and assuming no withdrawals or losses to follow up) this is estimated to be a total of
400 around 143,140 women per annum. A subset of around 30 participating women and
401 30 midwives, sonographers and obstetricians will be recruited to the nested
402 qualitative study, which is based in the Scottish sites.

403 *Inclusion criteria*

404 We will include all women delivering at one of the participating maternity units for the
405 duration of the study. Women who have been seen at any of the maternity units but
406 who deliver at home will not be included. The duration of the study will be 42 months

from the start of the trial (01/02/2014). For practical reasons, participants for the nested qualitative study will be recruited from the participating units in Scotland.

Exclusion criteria

We will exclude women as follows:

- Women for whom data on delivery outcomes is still unavailable four months after the date of delivery
- Women delivering in the “washout” period in each unit.

Members of the trial management group and participants who do not speak/understand English will be excluded from participating in the nested qualitative study.

Identifying participants

Women will be identified from those whose data is included in routine data returns from each unit. Potential participants for the nested qualitative study will be identified from those attending antenatal clinics in participating hospitals, and/or local staff.

Consenting participants

The main study is a stepped wedge cluster randomised trial of a package of care which would be introduced in many of the participating units regardless of whether the trial was on-going or not and the trial uses only routinely collected data on participants. The ethics committee indicated that formal individual patient consent is not necessary for the main trial. Participants in the nested qualitative study will be asked for individual consent.

Screening for eligibility

As participants are not directly recruited we will not perform any specific screening tests for this aspect of this project. Participants for the nested qualitative study will be: (i) Pregnant women attending hospitals who are participating in the main trial in

Scotland. Purposive sampling will ensure that the final sample set includes women who have and who have not experienced RFM, both before and after the introduction of the intervention; (ii) Hospital staff (including midwives, ultrasonographers and obstetricians/radiologists) working in participating hospitals in Scotland. There will be no specific screening tests for eligibility for the nested qualitative study, except that women who have experienced a stillbirth in the index pregnancy will not be approached.

Ineligible and non-recruited participants

Potential participants for the nested qualitative study who are not approached or who decline will have no specific interventions / procedures.

Withdrawal of Study Participants

The nature of a cluster randomised study is such that it is not possible for the participant to withdraw from the “cluster” unless she changes maternity unit part way through her pregnancy. We plan to collect routinely recorded anonymised data; patients have the right to opt out of having their data used – if this happens their data would be excluded from the study database (e.g. under the Confidentiality and Security advisory Group Report 2002 and the Data Protection Act (1998) requirements for fair processing of data). Participants in the nested qualitative study who wish to withdraw will be allowed to do so. Their data will be retained and used, unless they additionally indicate that they wish to withdraw their data.

RANDOMISATION

Randomisation Procedures

This is a cluster-randomised, stepped-wedge design trial wherein maternity units rather than individual patients are randomised. All units will implement the fetal movement monitoring intervention at some point during the trial; the random element is the time point at which this will occur, the so-called “step” of the stepped-wedge

design. Participating maternity units will be blinded to their randomly allocated time point until the time this is required to be revealed to enable the necessary training in the implementation of the intervention to be delivered. Primary and secondary outcomes of the trial will be gathered in a blinded manner via routinely collected data sources.

Maternity units which are in close proximity to each other will be grouped for the purposes of randomisation. This will assist with the feasibility of delivering the training for and implementation of the intervention. Furthermore, this local synchronisation of the intervention implementation will minimise the chances of contamination (introduction of the intervention prematurely) from maternity units which have already implemented the intervention to those not yet randomised.

The order in which the groups of maternity units step in to implement the intervention will be determined by computer generated random numbers from a uniform distribution. The randomisation list will be held by the Edinburgh Clinical Trials Unit (ECTU). The identities of the research team staff whose roles in the trial require them to be unblinded to randomisation codes will be recorded in the trial master file (TMF).

Treatment Allocation

Participating sites will be randomised to the intervention or conventional clinical management. All units will be providing conventional treatment at baseline according to local practice – this is the treatment established before the study starts. Sites will be randomised to “active” treatment in turn as described above. Active treatment will consist of a package of care consisting of a management plan for identification and delivery of the ‘at risk’ fetus, together with strategies for increasing pregnant women’s awareness of the need to report RFM early. The recommended management plan for identification and delivery of the “at risk” fetus is shown in Figure 2. Practice change in the active units will be achieved by: (i) written/email information to all clinicians (doctors, midwives and ultrasonographers) in each unit about the study protocol and

amendment of the local protocol for Reduced Fetal Movements (RFM) to that of the study protocol; (ii) a short web-based training package taking approximately one hour to complete for all clinicians in each centre and (iii) training /information sessions to run in each unit and (iv) posters in each unit to describe the practice change. Strategies for encouraging clinicians to increase pregnant women's awareness of fetal movement will include all the above and also a fetal movement leaflet for pregnant women (shown in Supplementary Information 1). The Norwegian quality improvement study showed inconclusive results regarding the effect of the intervention in non-European women.⁴¹ To attempt to address this, the AFFIRM information leaflet was available in 12 languages including: Arabic, Bengali, English, Hindi, Hungarian, Latvian, Lithuanian, Mandarin, Polish, Russian and Urdu. Furthermore, by including staff education which highlighted the need to ask women about fetal movements in routine antenatal consultations as many women as possible should have received information about what to do if they perceive RFM.

Once units have begun active treatment it is not anticipated that they will return to conventional treatment. We will conduct an audit of women presenting with reduced fetal movements and assess the proportion of staff completing the online training to assess the extent to which sites have followed the intervention plan. Units will be informed about treatment allocation as near as possible to the implementation of the "active" treatment. For practical purposes, we anticipate that each unit will need around three months' notice before the "active" treatment is introduced, hence units will be informed of the timing of their treatment allocation (step) three months before the active treatment is due to start. The treatment allocation will not be administered blind and there are no restrictions on concomitant care or other interventions during the study, hence there is no need for emergency unblinding and there are no stopping rules for the study.

511

512 DATA COLLECTION

513 For the main trial, data will be accessed from the information routinely collected
514 during the clinical management of the patient. For consistency, we will normally only
515 include data items which become available within four months after the delivery date
516 in question, although we may seek advice from the independently-chaired trial
517 steering committee (TSC) about exceptions as they arise. Different data sources will
518 be used for different regions of the study: (i) In Scotland the source data will be
519 SMR2 and the Scottish Birth record, (ii) In Ireland the source data will be the National
520 Perinatal Reporting System (NRPS http://www.esri.ie/health_information/nprs), (iii) In
521 Northern Ireland, the source data will be the Northern Ireland maternity Statistics
522 database (NIMATS), (iv) In England and Wales, the source data will be the ONS, or
523 other relevant body. Data will be collected retrospectively on an annual basis from all
524 sources. We will assume that data unavailable four months after the woman
525 delivered is likely to be unobtainable (but see note in Study Design section above).
526 Thus, data on the first year of the study will be collected at month 16; data on the
527 second year will be collected at month 28 etc.

528 Data are routinely collected. A formal request for data access will be made at the
529 start of the study. This will require (i) in Scotland – Privacy Advisory Committee
530 approval and a formal approach to NHS Scotland Information Services Division (ISD)
531 (ii) in Ireland a formal approach to NRPS (iii) NIMATS in Northern Ireland (iv) in
532 England and Wales a formal approach will be made to the relevant bodies.

533 Data will then be sent to the electronic Data Research and Innovation Service
534 (eDRIS) National Safe Haven (NHS National Services Scotland) by secure file
535 transfer protocol (or other similar) for storage and subsequent analysis within a
536 secure project area (dedicated to the AFFIRM study). Further information on the
537 National Safe Haven is available at [http://www.isdscotland.org/Products-and-](http://www.isdscotland.org/Products-and-Services/eDRIS/Becoming-an-eDRIS-User/#NSS-National-Safe-Haven)
538 [Services/eDRIS/Becoming-an-eDRIS-User/#NSS-National-Safe-Haven](http://www.isdscotland.org/Products-and-Services/eDRIS/Becoming-an-eDRIS-User/#NSS-National-Safe-Haven). Briefly, the

1
2
3 539 National Safe Haven is located on a secure server, in which trusted and authorised
4
5 540 researchers can analyse individual level data while maintaining the utmost
6
7 541 confidentiality. It is anticipated that all study analysis will be done within the Safe
8
9 542 Haven, using one of the available statistical packages (e.g. R, SPSS).
10
11 543 Identifiers on Scottish data within the National Safe Haven are concealed from
12
13 544 researchers. Data from outwith Scotland will be anonymised before submission to the
14
15 545 National Safe Haven. We propose that data submitted to the National Safe Haven
16
17 546 will be “anonymised” by the data provider. However, we propose that the
18
19 547 anonymisation link will be retained at the source so that it will be possible to re-link
20
21 548 data retrospectively. The rationale for retaining the ability of local data guardians to
22
23 549 re-link data is because it is important to retain the possibility of identifying individual
24
25 550 patients retrospectively. Examples include: (i) It is possible that some additional
26
27 551 important data may be available at a late stage on individual participants – e.g. in the
28
29 552 scenario where the woman or baby had a major adverse event and spent a long time
30
31 553 in hospital before discharge or death and (ii) Although our protocol and outcome
32
33 554 analysis does not require identifiable data, we believe this will be a ‘once in a lifetime’
34
35 555 study, and that subsequent secondary analyses could yield important information for
36
37 556 patients and for policy makers. If retrospective identification is not possible, this will
38
39 557 limit further analysis. One likely example of future analyses is to determine the effect
40
41 558 of the intervention on different causes of stillbirth. This is outwith the scope of the
42
43 559 current protocol, but could be done relatively straightforwardly, by linking nationally
44
45 560 recorded information on “cause” of stillbirth to our study database. We anticipate that
46
47 561 such additional analyses would require additional ethics approval, but without a
48
49 562 process by which to re-link data, it will not be possible to perform such subsequent
50
51 563 analyses.
52
53
54
55 564 All Investigators and study site staff involved with this study will comply with the
56
57 565 requirements of the Data Protection Act 1998 (or equivalent for those outwith the UK)
58
59
60

with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. Published results will not contain any personal data that could allow identification of an individual participant.

In addition to the data recorded above, all sites will be asked to provide a copy of their guidelines around (i) maternal awareness of RFM and (ii) management of women presenting with RFM. Copies of guidelines will be sought by the study office (a) at the start of the study (b) immediately before initiation of the intervention in each specific unit and (c) six months after initiation of the intervention in each specific unit.

For the nested qualitative study, we will perform interviews of healthcare workers and a small nested cohort of pregnant women about their experiences of fetal movement and of this intervention. We shall ensure a diversity of age and include nulliparous and multiparous women (n=30 in total). Ten interviews will be conducted with each of the following groups of health care providers: obstetricians, midwives and sonographers/radiologists. The interviews will take a semi-structured format (sensitising and piloting interviews will be conducted prior to the commencement of the trial and in the first month of the nested qualitative study). This format will ensure the same categories of data will be obtained from each participant but also allow individual responses to be fully explored.

584

585 **STATISTICS AND DATA ANALYSIS**

586 *Sample size calculation*

The sample size is the number of women delivering in hospitals participating in the study. This was initially planned to include sites in Scotland, totalling around 58,000 deliveries per year with 16 consultant led maternity units, 20 smaller units each delivering less than 350 babies per year, and seven units delivering less than five births per year. The units involved in Perinatal Ireland (an all-Ireland research

consortium across 7 academic sites in Ireland currently funded by the Health Research Board, Ireland) have 50,000 births per year with seven large sites. Combining one or two of the smaller units and one larger unit into a single “hospital group” for each local area could provide 24 hospital “groups” – the details of hospital groupings will be reviewed and finalised immediately prior to randomisation. In total, 36 sites expressed interested in participating in the study, although 2 were unable to participate in the study and withdrew before randomisation. In total, 34 units were randomised, these were situated throughout the UK and Ireland (10 in England, 4 in Ireland, 15 in Scotland and 5 in Wales) with 143,140 births per annum.

We calculated statistical power using the methodology for stepped wedge designs proposed in Hussey and Hughes (2007).⁴² First, we analysed stillbirth event data from the Scottish Perinatal and Infant Mortality and Morbidity Report (SPIMMR) covering years 2005-2010¹⁷ to determine estimates of between- and within-unit variability in stillbirth rate. Analysis was by generalized linear mixed model for binary outcomes. The power calculation, as per equations (#7) and (#8) in⁴² assumed: significance level 5%; analysis by generalized linear mixed model; deliveries equally distributed across hospital groupings; baseline stillbirth rate 0.438%¹⁷; between-cluster variance 0.00816.

Finally, the statistical power depends on the number of groups in which the intervention is implemented at each stage of the stepped wedge design and the duration of recruitment at each “step”. Our study design proposes sequential introduction of the intervention into three hospital groups at a time at four month intervals over a 32 month period. It is anticipated that unavailability of data and women asking to withdraw their data will be less than 1%. This would give 89.9% power to detect a 30% risk reduction under the intervention and 77.0% power to detect a 25% reduction. A 30% risk reduction was seen in the Norwegian study; the anticipated effect sizes of 25% and 30% relative reduction take into account that the

1
2
3 619 intervention will not have the power to reduce all stillbirths, since 20% of stillbirths in
4
5 620 Ireland ⁴³ and 15% in Scotland ¹⁷ are associated with congenital anomaly.
6
7

8 621 *Proposed analyses*
9

10 622 For the binary primary and secondary outcomes, data will be analysed by
11
12 623 generalized linear mixed model with a random effect for hospital and fixed effects for
13
14 624 the intervention implementation and study time period. A site by intervention
15
16 625 interaction random effect will be included in the model and retained if it explains an
17
18 626 important proportion of the variability in outcomes. The primary analysis of data will
19
20 627 be on an intention to treat basis (the design of the trial means it is not possible to
21
22 628 determine individual patient /caregiver compliance with the intervention). An “on
23
24 629 treatment” variable will be calculated for which women will be grouped as active or
25
26 630 control according to when the intervention was actually implemented in their site,
27
28 631 instead of when the site was randomised to implement the intervention. The primary
29
30 632 outcome will be reanalysed in two sensitivity analyses. Firstly, we will perform the
31
32 633 analysis according to the actual timing of the implementation of the intervention
33
34 634 rather than the randomised timing of the intervention using the “on treatment”
35
36 635 classification. Secondly, we will perform the analysis in the subgroup of sites who
37
38 636 were deemed to have implemented the intervention effectively according to the
39
40 637 perception of the Principal Investigator at each site. The accuracy of this perception
41
42 638 will be confirmed with the findings of a site audit (details in Supplementary
43
44 639 Information 2). There will be no attempt to correlate the impact of the intervention
45
46 640 according to the results of the site audit.
47

48
49 641 There are no planned imputations for missing data. However, if the missing data rate
50
51 642 for smoking status during pregnancy is relatively high an imputation technique will be
52
53 643 devised. The imputation method will be informed using smoking history at booking
54
55 644 and age at delivery ⁴⁴. A pre-specified subgroup analysis will be performed for babies
56
57 645 with and without congenital anomalies, and will be implemented by testing for an
58
59
60

646 intervention by congenital anomaly interaction added to the generalised linear mixed
647 model described above. No formal interim analyses for efficacy or safety will be
648 performed. A full statistical analysis plan will be finalised prior to locking of the study
649 database.

650 *Qualitative Data*

651 For the nested qualitative study, the data will be audio recorded and transcribed.
652 The data will be coded thematically and an analytical framework developed to make
653 sense of patient experience of fetal movement and the intervention and also health
654 care providers' perspectives and experiences. NVivo will be utilised to support the
655 analysis.

656 *Process outcomes*

657 The process outcomes being assessed by the (rates of induction of labour, number
658 of women presenting with reduced fetal movements, interval between perceiving fetal
659 movements and presenting to hospital) will be analysed using the same methods as
660 for the main trial, with the exception of the continuous outcome (interval between
661 perceiving fetal movements and presenting to hospital) which will be analysed using
662 a normal linear mixed model.

663 **ADVERSE EVENTS**

664 This is not a Clinical Trial of an Investigational Medicinal Product (CTIMP) so adverse
665 events will not be formally reported. Stillbirth and other measures of fetal and
666 maternal morbidity are outcomes of the study. The purpose of the intervention is to
667 reduce such adverse events. Therefore, due to the low risks for this trial, a separate
668 DMC is not required and the Trial Steering Committee (TSC) will cover any
669 responsibilities normally allocated to a DMC. If considered necessary, the TSC may
670 review unblinded data for the study, including morbidity and mortality indices. No
671 other adverse event reporting will be undertaken.

672

For peer review only

673 **TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS**

674 The trial will be coordinated by a Project Management Group, consisting of the grant
675 holders and the Trial Manager. The Chief Investigator (JN) will lead the project
676 management group. The Trial Manager will oversee the study and will be
677 accountable to the Chief Investigator. A TSC will be established to oversee the
678 conduct and progress of the trial. The terms of reference and a draft template for
679 reporting will be ratified in one of the early meetings of the TSC.

680 Investigators and institutions involved in the study will permit trial related monitoring
681 and audits on behalf of the co-sponsors (ACCORD: Academic and Clinical Central
682 Office for Research & Development - Joint office for University of Edinburgh and
683 NHS Lothian, Sponsor contact: ray.french@ed.ac.uk), research ethics committee
684 (REC) review, and regulatory inspection(s). In the event of an audit or monitoring, the
685 Investigator agrees to allow the representatives of the sponsor direct access to all
686 study records and source documentation. In the event of regulatory inspection, the
687 Investigator agrees to allow inspectors direct access to all study records and source
688 documentation.

690 *Study monitoring and audit*

691 The sponsor determined that as no individual participants were recruited to the
692 intervention, and it was not a clinical trial of an investigational medicinal product
693 (CTIMP) no formal monitoring and audit was required.

695 *Good Clinical Practice and Ethical Conduct*

696 The study will be conducted in accordance with the principles of the research
697 governance framework operational and good clinical practice in the relevant country.
698 A favorable ethical opinion has been obtained from the Scotland A REC (Reference

13/SS/0001) and local research and development approval has been obtained prior to commencement of the study.

Local study investigator(s) will be appointed to each site (or for small units, groups of sites). S/he will be responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments.

STUDY CONDUCT RESPONSIBILITIES

Protocol amendments

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the participant in the case of an urgent safety measure, will be reviewed and approved by the Chief Investigator and Sponsor. Amendments to the protocol will be submitted in writing to the appropriate REC and local Research and Development (R&D) department for approval prior to participants being enrolled into an amended protocol.

Protocol violations and deviations

Investigators will not implement any deviation from the protocol without agreement from the Chief Investigator and appropriate REC and R&D department approval except where necessary to eliminate an immediate hazard to trial participants. In the event that an Investigator needs to deviate from the protocol, the nature of and reasons for the deviation will be recorded. If this necessitates a subsequent protocol amendment, this will be submitted to the REC, and local R&D department for review and approval if appropriate.

Serious breach requirements

A serious breach is one which is likely to effect to a significant degree (a) the safety or physical or mental integrity of the participants of the trial; or b) the scientific value

of the trial. If a potential serious breach is identified by the Chief investigator, Principal Investigator or delegates, the co-sponsors (accord.seriousbreach@ed.ac.uk) will be notified within 24 hours. It will be the responsibility of the co-sponsors to assess the impact of the breach on the scientific value of the trial, to determine whether the incident constitutes a serious breach and, if so, report it to the REC.

All violations will be assessed by the sponsor(s) to ascertain if they meet the criteria for a serious breach. If the sponsor(s) deem the incident to be a violation that does not constitute a serious breach from the protocol when identified, corrective and preventative actions will be taken where appropriate and they will be recorded in file notes, held within the TMF and ISF.

Study record retention

All study documentation will be kept for a minimum of 5 years from the protocol defined end of study point. When the minimum retention period has elapsed, study documentation will not be destroyed without permission from the sponsor.

End of study

The end of study date was finalised in the protocol after the study commenced; the agreed end of study date is 31/12/2016. The Investigators and/or the trial steering committee and/or the co-sponsor(s) have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the REC within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants of the premature study closure and ensure that the appropriate follow up is arranged for all participants involved. A summary report of the study will be provided to the REC and Regulatory Authority within 1 year of the end of the study.

750

751 **REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS**

752 Ownership of the data arising from this study resides with the study team. On
753 completion of the study, the study data will be analysed and tabulated, and a clinical
754 study report will be prepared in accordance with good clinical practice guidelines.
755 The clinical study report will be used as the basis for publication and presentation at
756 scientific meetings. Investigators have the right to publish orally or in writing the
757 results of the study. Summaries of results will also be made available to Investigators
758 for dissemination within their clinics (where appropriate and according to their
759 discretion).

760

761 **DISCUSSION**

762 The data provided by this study will inform the information given to women about
763 reduced fetal movements and their management when they present to maternity
764 services; which has been recurrently identified by Confidential Enquiries into
765 antepartum stillbirths as suboptimal^{27 28}. Data from the AFFIRM study will be able to
766 be compared to results from two other active studies which aim to improve mothers
767 awareness and reporting of reduced fetal movements. My Babies Movement
768 (ACTRN 12614000291684) is stepped-wedge cluster trial of a mobile phone
769 application to help women get to know their baby's movements, to be mindful of
770 movements every day and not to wait to report concerns to their maternity care
771 provider. The Mindfetalness study (NCT02865759) is a cluster trial of 39,000 women
772 randomised to routine antenatal care or the Mindfetalness brochure and website.⁴⁵
773 Women participating in the Mindfetalness process will spend 15 minutes each day
774 getting to know their babies movements and will specifically be encouraged to
775 contact their health provider if their perceive reduced fetal movements. This primary

outcome of this study is an Apgar score <7 at 5 minutes; stillbirth and perinatal deaths will be recorded as tertiary endpoints of this study.⁴⁵ These large studies will provide much needed robust evidence to determine whether increased maternal awareness of reduced fetal movements combined with a standardised management protocol to identify acute or chronic fetal compromise can reduce stillbirth³³.

PEER REVIEW

This project has been peer reviewed internally, and was externally peer reviewed during the process of securing funding from the Chief Scientist's Office of the Scottish Government, Tommy's and Sands.

FUNDING

The AFFIRM study is investigator initiated and funded by Chief Scientist Office, Scottish Government (CZH/4/882), Tommy's and Sands, the Stillbirth and Neonatal Death Charity. CJW was supported in this work by NHS Lothian via the Edinburgh Clinical Trials Unit. AEPH is supported by a Clinician Scientist fellowship from the National Institute for Health Research (NIHR; CS-2013-009). This protocol presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

ACKNOWLEDGEMENTS

The authors would like to acknowledge the support of Perinatal Ireland and Dr Mary Higgins (University College Dublin, National Maternity Hospital, Dublin).

CONTRIBUTIONS

Contributors AEPH, CJW, SJES, CJC, SCB, MRD, SW and JEN were involved in developing the trial design. AEPH, CJW, SJES, AR and JEN were involved in drafting and revision of the article. CJW and AR were involved in drafting the statistical aspects of the protocol. JS provided feedback on behalf of a stakeholder organisation. AEPH, CJW, SJES, CJC, SCB, JFF, MG, AH, FMM, EM, AR, MRD, JS, SW and JEN were involved in preparing the overall study design. AEPH, JEN and MRD prepared education videos for online training. AEPH, SJES, SJS, MG, AH, FMM and JEN facilitated recruitment of sites. AEPH, CJW, SJES, CJC, SCB, JFF, MG, AH, FMM, EM, AR, MRD, JS, SW and JEN will be involved in the collection, management, analysis and interpretation of data and final writing of the trial report.

COMPETING INTERESTS

None declared.

815 **ABBREVIATIONS**

816	ACCORD	Academic and Clinical Central Office for Research & Development -
817		Joint office for University of Edinburgh and NHS Lothian
818	BMI	Body Mass Index
819	CTG	Cardiotocograph
820	CTIMP	Clinical Trial of an Investigational Medicinal Product
821	ECTU	Edinburgh Clinical Trials Unit
822	FGR	Fetal growth restriction
823	MHRA	Medicines and Healthcare products Regulatory Agency
824	NICE	National Institute for Health and Social Care Excellence
825	NIHR	National Institute for Health Research
826	NIMATS	Northern Ireland Maternity Statistics database
827	NRPS	National Perinatal Reporting System
828	ONS	Office of National Statistics
829	PSANZ	Perinatal Society of Australia and New Zealand
830	RCOG	Royal College of Obstetricians and Gynaecologists
831	R&D	Research and Development
832	REC	Research Ethics Committee
833	RFM	Reduced Fetal Movements
834	SPIMMR	Scottish Perinatal and Infant Mortality and Morbidity Report
835	TMF	Trial Master File
836	TSC	Trial Steering Committee
837	WHO	World Health Organisation

838

839

REFERENCES

1. Still-Birth Definition Act Great Britain Curr Law Statut Annot GB, 1992:1.
2. Flenady V, Wojcieszek AM, Middleton P, Ellwood D, Erwich JJ, Coory M, et al. Stillbirths: recall to action in high-income countries. *Lancet* 2016;387(10019):691-702.
3. Flenady V, Koopmans L, Middleton P, Froen JF, Smith GC, Gibbons K, et al. Major risk factors for stillbirth in high-income countries: a systematic review and meta-analysis. *Lancet* 2011;377(9774):1331-40.
4. Manktelow BM, Smith LK, Seaton SE, Hyman-Taylor P, Kurinczuk JJ, Field DJ, et al. Perinatal Mortality Surveillance Report - UK Perinatal Deaths for births from January to December 2014. Leicester:: The Infant Mortality and Morbidity Group, Department of Health Sciences, University of Leicester., 2016.
5. Lawn JE, Blencowe H, Pattinson R, Cousens S, Kumar R, Ibiebele I, et al. Stillbirths: Where? When? Why? How to make the data count? *Lancet* 2011;377(9775):1448-63.
6. Flenady V, Middleton P, Smith GC, Duke W, Erwich JJ, Khong TY, et al. Stillbirths: the way forward in high-income countries. *Lancet* 2011;377(9778):1703-17.
7. Heazell AE, Whitworth MK, Whitcombe J, Glover SW, Bevan C, Brewin J, et al. Research priorities for stillbirth: process overview and results from UK Stillbirth Priority Setting Partnership. *Ultrasound Obstet Gynecol* 2015;46(6):641-7.
8. Heazell AE, Froen JF. Methods of fetal movement counting and the detection of fetal compromise. *J Obstet Gynaecol* 2008;28(2):147-54.
9. Stacey T, Thompson JM, Mitchell EA, Ekeroma AJ, Zuccollo JM, McCowan LM. The Auckland Stillbirth study, a case-control study exploring modifiable risk factors for third trimester stillbirth: methods and rationale. *The Australian & New Zealand journal of obstetrics & gynaecology* 2011;51(1):3-8.

1
2
3 868 10. Warland J, O'Brien LM, Heazell AE, Mitchell EA. An international internet survey
4
5 869 of the experiences of 1,714 mothers with a late stillbirth: the STARS cohort
6
7 870 study. *BMC pregnancy and childbirth* 2015;15:172.
8
9 871 11. Warrander LK, Heazell AE. Identifying placental dysfunction in women with
10
11 872 reduced fetal movements can be used to predict patients at increased risk of
12
13 873 pregnancy complications. *Medical hypotheses* 2011;76(1):17-20.
14
15 874 12. Vintzileos AM, Fleming AD, Scorza WE, Wolf EJ, Balducci J, Campbell WA, et al.
16
17 875 Relationship between fetal biophysical activities and umbilical cord blood gas
18
19 876 values. *Am J Obstet Gynecol* 1991;165(3):707-13.
20
21 877 13. Warrander LK, Batra G, Bernatavicius G, Greenwood SL, Dutton P, Jones RL, et
22
23 878 al. Maternal perception of reduced fetal movements is associated with altered
24
25 879 placental structure and function. *PloS one* 2012;7(4):e34851.
26
27 880 14. Winje BA, Roald B, Kristensen NP, Froen JF. Placental pathology in pregnancies
28
29 881 with maternally perceived decreased fetal movement--a population-based
30
31 882 nested case-cohort study. *PloS one* 2012;7(6):e39259.
32
33 883 15. Holm Tveit JV, Saastad E, Stray-Pedersen B, Bordahl PE, Froen JF. Maternal
34
35 884 characteristics and pregnancy outcomes in women presenting with decreased
36
37 885 fetal movements in late pregnancy. *Acta Obstet Gynecol Scand*
38
39 886 2009;88(12):1345-51.
40
41 887 16. Ptacek I, Sebire NJ, Man JA, Brownbill P, Heazell AE. Systematic review of
42
43 888 placental pathology reported in association with stillbirth. *Placenta*
44
45 889 2014;35(8):552-62.
46
47 890 17. Healthcare Improvement Scotland. Scottish Perinatal and Infant Mortality and
48
49 891 Morbidity Report 2010. Edinburgh: Healthcare Improvement Scotland, 2012.
50
51 892 18. Gardosi J, Kady SM, McGeown P, Francis A, Tonks A. Classification of stillbirth
52
53 893 by relevant condition at death (ReCoDe): population based cohort study. *BMJ*
54
55 894 *(Clinical research ed* 2005;331(7525):1113-7.
56
57
58
59
60

- 1
2
3 895 19. Saastad E, Winje BA, Stray Pedersen B, Froen JF. Fetal movement counting
4
5 896 improved identification of fetal growth restriction and perinatal outcomes--a
6
7 897 multi-centre, randomized, controlled trial. *PloS one* 2011;6(12):e28482.
8
9 898 20. Mangesi L, Hofmeyr GJ, Smith V, Smyth RM. Fetal movement counting for
10
11 899 assessment of fetal wellbeing. *Cochrane Database Syst Rev*
12
13 900 2015(10):CD004909.
14
15 901 21. Grant A, Elbourne D, Valentin L, Alexander S. Routine formal fetal movement
16
17 902 counting and risk of antepartum late death in normally formed singletons.
18
19 903 *Lancet* 1989;2(8659):345-9.
20
21 904 22. National Institute for Health and Clinical Excellence. Clinical Guideline 62 -
22
23 905 Antenatal care: routine care for the health pregnant woman. London: National
24
25 906 Institute for Health and Clinical Excellence, 2008.
26
27 907 23. Sergent F, Lefevre A, Verspyck E, Marpeau L. Decreased fetal movements in the
28
29 908 third trimester: what to do? *Gynecol Obstet Fertil* 2005;33(11):861-9.
30
31 909 24. Froen JF, Heazell AE, Tveit JV, Saastad E, Fretts RC, Flenady V. Fetal
32
33 910 movement assessment. *Seminars in perinatology* 2008;32(4):243-6.
34
35 911 25. Saastad E, Vangen S, Froen JF. Suboptimal care in stillbirths - a retrospective
36
37 912 audit study. *Acta Obstet Gynecol Scand* 2007;86(4):444-50.
38
39 913 26. Froen JF, Arnestad M, Frey K, Vege A, Saugstad OD, Stray-Pedersen B. Risk
40
41 914 factors for sudden intrauterine unexplained death: epidemiologic
42
43 915 characteristics of singleton cases in Oslo, Norway, 1986-1995. *Am J Obstet*
44
45 916 *Gynecol* 2001;184(4):694-702.
46
47 917 27. Confidential Enquiry into Stillbirths and Deaths in Infancy. 8th Annual Report, 1
48
49 918 January–31 December 1999. London: Maternal and Child Health Research
50
51 919 Consortium, 2001.
52
53 920 28. Draper ES, Kurinczuk JJ, Kenyon S, MBRRACE-UK. obo. MBRRACE-UK
54
55 921 Perinatal Confidential Enquiry: Term, singleton, normally formed, antepartum
56
57
58
59
60

stillbirth. Leicester: The Infant Mortality and Morbidty Studies, Department of Health Sciences, University of Leicester, 2015.

29. Linde A, Pettersson K, Radestad I. Women's Experiences of Fetal Movements before the Confirmation of Fetal Death--Contractions Misinterpreted as Fetal Movement. *Birth* 2015;42(2):189-94.

30. Preston S, Mahomed K, Chadha Y, Flenady V, Gardener G, MacPhail J, et al. Clinical practice guideline for the management of women who report decreased fetal movements. Brisbane,: Australia and New Zealand Stillbirth Alliance, 2010.

31. Royal College Of Obstetricians and Gynaecologists. Management of Reduced Fetal Movements. London: RCOG, 2011.

32. Tveit JV, Saastad E, Stray-Pedersen B, Bordahl PE, Flenady V, Fretts R, et al. Reduction of late stillbirth with the introduction of fetal movement information and guidelines - a clinical quality improvement. *BMC pregnancy and childbirth* 2009;9:32.

33. Hofmeyr GJ, Novikova N. Management of reported decreased fetal movements for improving pregnancy outcomes. *Cochrane Database Syst Rev* 2012;4:CD009148.

34. Froen JF, Tveit JV, Saastad E, Bordahl PE, Stray-Pedersen B, Heazell AE, et al. Management of decreased fetal movements. *Seminars in perinatology* 2008;32(4):307-11.

35. Dutton PJ, Warrander LK, Roberts SA, Bernatavicius G, Byrd LM, Gaze D, et al. Predictors of poor perinatal outcome following maternal perception of reduced fetal movements--a prospective cohort study. *PloS one* 2012;7(7):e39784.

36. Royal College Of Obstetricians and Gynaecologists. The Investigation And Management Of The Small-For-Gestational-Age Fetus. London: RCOG, 2013.

- 1
2
3 949 37. Heazell AE, Green M, Wright C, Flenady V, Froen JF. Midwives' and
4
5 950 obstetricians' knowledge and management of women presenting with
6
7 951 decreased fetal movements. *Acta Obstet Gynecol Scand* 2008;87(3):331-9.
8
9 952 38. Jokhan S, Whitworth MK, Jones F, Saunders A, Heazell AE. Evaluation of the
10
11 953 quality of guidelines for the management of reduced fetal movements in UK
12
13 954 maternity units. *BMC pregnancy and childbirth* 2015;15:54.
14
15 955 39. Tveit JV, Saastad E, Stray-Pedersen B, Bordahl PE, Flenady V, Fretts R, et al.
16
17 956 Erratum to: Reduction of late stillbirth with the introduction of fetal movement
18
19 957 information and guidelines - a clinical quality improvement. *BMC pregnancy*
20
21 958 *and childbirth* 2010;10:49.
22
23 959 40. Winje BA, Wojcieszek AM, Gonzalez-Angulo LY, Teoh Z, Norman J, Froen JF, et
24
25 960 al. Interventions to enhance maternal awareness of decreased fetal
26
27 961 movement: a systematic review. *Bjog* 2016;123(6):886-98.
28
29 962 41. Saastad E, Tveit JV, Flenady V, Stray-Pedersen B, Fretts RC, Bordahl PE, et al.
30
31 963 Implementation of uniform information on fetal movement in a Norwegian
32
33 964 population reduced delayed reporting of decreased fetal movement and
34
35 965 stillbirths in primiparous women - a clinical quality improvement. *BMC*
36
37 966 *research notes* 2010;3(1):2.
38
39 967 42. Hussey MA, Hughes JP. Design and analysis of stepped wedge cluster
40
41 968 randomized trials. *Contemp Clin Trials* 2007;28(2):182-91.
42
43 969 43. ESRI Health Research and Information Division. Perinatal Statistics Report 2009,
44
45 970 2011.
46
47 971 44. Tominey E. Maternal smoking during pregnancy and early child outcomes.
48
49 972 Discussion Paper no. 828. London: Centre for Economic Performance,
50
51 973 London School of Economics., 2007.
52
53 974 45. Radestad I, Akselsson A, Georgsson S, Lindgren H, Pettersson K, Steineck G.
54
55 975 Rationale, study protocol and the cluster randomization process in a
56
57 976 controlled trial including 40,000 women investigating the effects of
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

977 mindfetalness. *Sexual & reproductive healthcare : official journal of the*
978 *Swedish Association of Midwives* 2016;10:56-61.
979
980
981

For peer review only

FIGURE LEGENDS

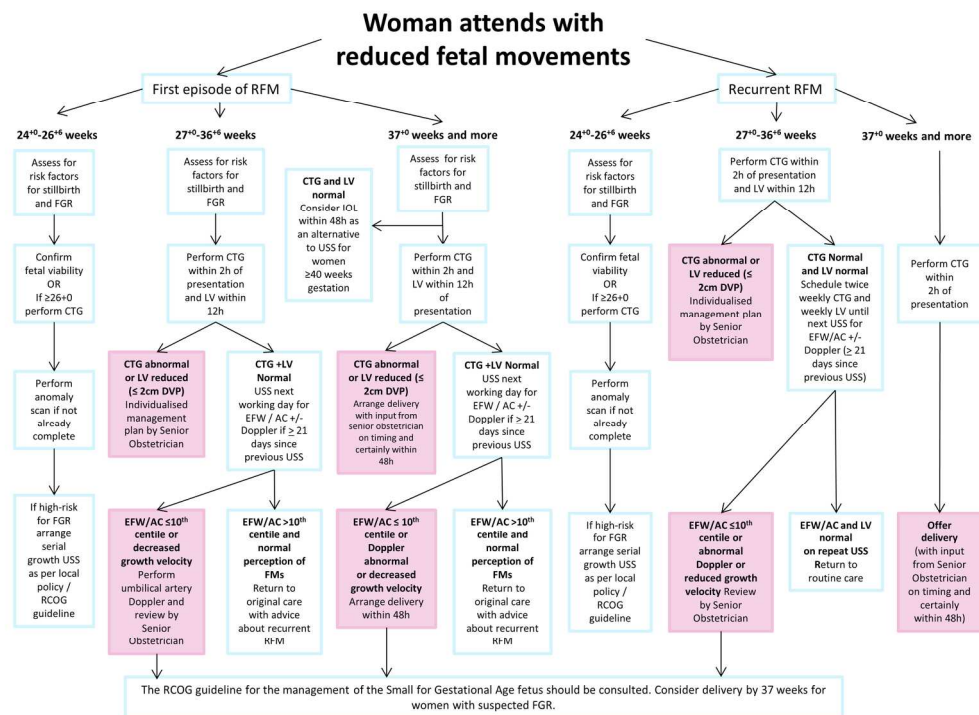
Figure 1 - Stepped wedge design. The shaded areas (both light and dark) indicate periods in which the interventions are being implemented. The lighter areas indicate the “transition” period during which data will not be collected for the control or intervention group. The order in which hospital groupings implement the interventions will be determined via randomization.

Figure 2 – Flow chart for the management of women presenting with reduced fetal movements for sites implementing the AFFIRM study. Abbreviations: AC - abdominal circumference, CTG- cardiotocograph, DVP - deepest vertical pool, EFW - estimated fetal weight, FGR - fetal growth restriction, LV - liquor volume, RFM - reduced fetal movement, USS - ultrasound scan.

Hospital groupings	Months since Start of Trial								
	1-4	5-8	9-12	13-16	17-20	21-24	25-28	29-32	33-36
1-3									
4-6									
7-9									
10-12									
13-15									
16-18									
19-21									
22-24									

Stepped wedge design. The shaded areas (both light and dark) indicate periods in which the interventions are being implemented. The lighter areas indicate the “transition” period during which data will not be collected for the control or intervention group. The order in which hospital groupings implement the interventions will be determined via randomization.

190x142mm (300 x 300 DPI)



Flow chart for the management of women presenting with reduced fetal movements for sites implementing the AFFIRM study. Abbreviations: AC - abdominal circumference, CTG- cardiotocograph, DVP - deepest vertical pool, EFW - estimated fetal weight, FGR - fetal growth restriction, LV - liquor volume, RFM - reduced fetal movement, USS - ultrasound scan.

190x142mm (300 x 300 DPI)

WHO TO CONTACT IF YOU ARE CONCERNED:
(space for sticky with local contact information)



APS Group Scotland
DPPAS33137
Version 3 March 2015



In touch with
YOUR BABY

A guide to your baby's
movements during
pregnancy



For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>

**Why are my baby's
movements important?**

**Why are we asking women
to get to know their baby's
movements?**

One of the easiest ways to tell if your baby is healthy is to be aware of how much he or she is moving. Every baby is different and we are asking women to take time to become familiar with their baby's own individual pattern of movements. A reduction or change in **your** baby's movements is what is important.

**What can affect my baby's
movements?**

You are less likely to be aware of your baby's movements when active or busy. Some drugs e.g. strong pain relief or sedatives can get into an unborn baby's circulation and affect the movements. Alcohol and smoking (active and passive smoking) may also affect the baby.

**Why are my baby's
movements important?**

If you notice your baby is moving less than usual, or the pattern of movements has changed, this could be the first sign that your baby may not be well or is not growing properly in the womb. Research has shown that a reduction in the baby's movements may indicate an increased risk of stillbirth. You may hear your midwife or doctor referring to 'reduced fetal movement', or RFM for short.

What are the risks of stillbirth?

Stillbirth affects one in 200 babies after 24 weeks gestation and is one of the most common of the serious complications of pregnancy, affecting the lives of around 4,000 families every year in the UK.

One of the easiest ways to tell if your baby is healthy is to see how much he or she is moving. This booklet tells you what to look out for during your pregnancy.

Every baby is different. It is good to get to know your baby's own movements and the pattern of their sleeping and waking and report to us if you notice a reduction in these movements.



18-24
WEEKS



Most women begin to feel their baby move between 18-24 weeks. At first it may feel like 'bubbles', 'flutterings' or 'like trapped wind'. These are often very short and stop and start. It might take you a little while to be sure what you are feeling. But you will soon get to know the feelings. If this is your second baby, you will know what to look out for and may recognise your baby moving sooner.

Everyone is different when it comes to their movements. There are many reasons you might not feel movements as early as you expect. This includes your body weight, the position of your baby and the location of your placenta. What is important is your baby is growing well. Your midwife will be able to discuss this with you further at your 22 week check.

Try to get to know the times of the day when you are most likely to feel your baby move.



24-36
WEEKS



You will have your own way of describing your baby's own movements. Women often describe their baby's movements as 'rolling', 'kicking', 'pushing', 'jabs', 'elbowing' and 'stretches'.

Between 24-36 weeks you will start to recognise your baby's movements more quickly and become more used to the feeling. It is usually easier to feel your baby's movements when you are lying down, e.g. at night time. It is harder to feel your baby move when you are on your feet and moving around.

Try to get to know the times of the day you are most likely to feel your baby move. This will help you to know if he or she is moving less than normal or if movements have stopped.

Occasionally your baby will get hiccups. These do not count as movements. If you are unsure what you should expect when your baby hiccups, speak to your midwife.



Appendix 3 - Audit of compliance with AFFIRM protocol

Compliance with the AFFIRM management protocol (the management plan for women presenting with reduced fetal movement) will be determined by to means:

A) Telephone / email contact with Principal Investigators at each site to determine which aspects of the AFFIRM protocol have been implemented effectively. This will involve email contact with Principal Investigators to alert them to the request for information, an email detailing the information required, and then a phone call to elicit the information (unless it had already been supplied). Investigators will be asked which of the following elements they had implemented: issuing leaflets to all pregnant women, cardiotocography within 2 hours of presentation, measurement of amniotic fluid volume within 12 hours of presentation, growth scan by the next working day for all women presenting with reduced fetal movement (and who had not had a growth scan within the last three weeks, or who were not being induced within 48 hours), and induction of labour within 48 hours for women presenting with recurrent reduced fetal movement at or after 37 weeks gestation. “Effective implementation” was defined as the above management for 4/5 of these elements for 80% or more of the time.

B) An audit to determine whether the perception of the site Principal Investigator is supported by review of actual decision making will be performed for the following elements: cardiotocography within 2 hours of presentation, measurement of amniotic fluid volume within 12 hours of presentation, growth scan by the next working day for all women presenting with reduced fetal movement (and who had not had a growth scan within the last three weeks, or who were not being induced within 48 hours), and induction of labour within 48 hours for women presenting with recurrent reduced fetal movement at or after 37 weeks gestation.

This will be conducted by asking sites to complete an audit of the management of all women presenting with reduced fetal movement over the course of one calendar month. Sites will be asked to complete an audit form for each participant. The audit form template (see below) has been generated by the central

AFFIRM study team; anonymized forms will be analysed centrally. There will not be an attempt to corroborate Principal Investigator perception of the proportion of women who were given leaflets, nor will there be any attempt to incorporate the proportion of staff who had completed the e-learning package into analysis of whether any specific site has implemented the intervention or not.

For peer review only

Compliance with AFFIRM reduced fetal movements protocol, One month data collection AUDIT [Month & Year] Unit name: [Name of Hospital]

If you assess a woman with reduced fetal movements (RFM), please complete the questions below. Do not worry if the woman has been seen in other areas of the hospital by other staff, we would rather have multiple reports for the same woman than miss episodes of RFM.

INSERT Patient Sticker (or WRITE name and CHI /NHS number)				AREA WHERE SEEN (CIRCLE) Triage / Labour ward / Day Assessment Unit (DAU) Other (specify area i.e. antenatal ward): _____							
Date and time of presentation with reduced fetal movements.	DATE: ____/____/____ TIME ____:____ am / pm				GESTATION AND EDD:	____ WEEKS ____ DAYS EDD: _____					
Referred by (TICK BOX):	Self	Community Midwife	GP	ANC	Triage	DAU	Other (specify: _____)				
What was the primary reason for attending/phoning? (TICK BOX):	Reduced Fetal Movements				Other (specify: _____)						
How many times has the woman attended before this visit, with RFM? (TICK BOX):	None – first attendance		Once previously		Unknown	Multiple times (please provide the gestation at each presentation i.e. 30+6)	1	2	3	4	5
What was the time interval from the woman first being aware of reduced fetal movements and attending the hospital (in hours)?						HOURS: _____					
Has she been given a leaflet “Your baby’s movements in pregnancy”? (TICK BOX):	Yes – she already has one		Yes – I have given one to her today			Locally Created Leaflet Given	NO				
Has this woman had a growth USS in this pregnancy? (TICK BOX):	No, she has not had a growth scan		Yes, within the last 3 weeks (date of scan): DATE: ____/____/____			Yes, but more than 3 weeks ago (date of scan): DATE: ____/____/____					

CONTINUATION: NHS/ CHI NUMBER:

Are any of the following risk factors for Fetal growth restriction present (CIRCLE all that apply)?							
Age ≥40 or ≤16	Smoker ≥20cpd	Known or suspected growth restriction	Congenital anomaly	Raised BP (essential hypertension, pre-eclampsia or pregnancy induced hypertension)	Previous pre-eclampsia	Diabetes or gestational diabetes	Previous FGR or stillbirth
What investigations were conducted during this episode of reduced fetal movement?							
Please record below the date and time that these investigations were completed or indicate if not performed.						Please provide the results (CIRCLE):	
CTG	Not performed <input type="checkbox"/>	DATE: __/__/____	TIME: ____:____ am/pm	Normal / Suspicious / Pathological			
		<u>Computerised CTG</u> : YES / NO (CIRCLE)					
Liquor volume assessment on scan	Not performed <input type="checkbox"/>	DATE: __/__/____	TIME: ____:____ am/pm	Normal / Reduced / Increased			
Growth scan	Not performed <input type="checkbox"/>	DATE: __/__/____	TIME: ____:____ am/pm	Normal / EFW < 10 th centile/ AC < 10 th centile / EFW and AC < 10 th centile			
Umbilical Artery Doppler	Not performed <input type="checkbox"/>	DATE: __/__/____	TIME: ____:____ am/pm	Normal/.> 95 th centile/absent EDF/reversed EDF			
MCA Doppler	Not performed <input type="checkbox"/>	DATE: __/__/____	TIME: ____:____ am/pm	Normal/<5 th centile			
DELIVERY METHOD (If available)							
Was the woman offered induction of labour	YES / NO (CIRCLE) IF Yes, please provide date, time and method of the induction:			DATE: ____/____/____ TIME: ____:____ am/pm			
Was the woman offered elective caesarean section as a result of the reduced fetal movement?	YES / NO (CIRCLE) IF Yes, please provide date, time and reason:			DATE: ____/____/____ TIME: ____:____ am/pm Please provide the reason for the elective Caesarean section:			



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	___ Page 1 ___
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	___ Page 4 ___
	2b	All items from the World Health Organization Trial Registration Data Set	_Included throughout protocol_
Protocol version	3	Date and version identifier	___ Page 4 ___
Funding	4	Sources and types of financial, material, and other support	___ Page 28 ___
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	_Names and affiliations Page 1 and 2; Contributions Page 28_
	5b	Name and contact information for the trial sponsor	___ Page 24 ___
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	_Not applicable_

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	___Page 24___
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	__Pages 5-11__
	6b	Explanation for choice of comparators	__Pages 8-9___
Objectives	7	Specific objectives or hypotheses	__Pages 11-12__
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	__Pages 13- 14 and Figure 1 ___
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	__Pages 13 & 16__
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	__Pages 14-15__
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	__Pages 17-18 and Figure 2__
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	__Not applicable in AFFIRM trial__
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	__Pages 17-18__
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	__Not applicable__

1				
2				
3	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	__Pages 12-13__
4				
5				
6				
7				
8	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	__Randomisation by site explained in Figure 1 and Pages 13-14__
9				
10				
11				
12				
13	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	__Pages21-22 __
14				
15				
16				
17	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	__Page 22 ____
18				
19	Methods: Assignment of interventions (for controlled trials)			
20				
21	Allocation:			
22				
23	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	__Page 17 ____
24				
25				
26				
27				
28				
29	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	__Page 17 ____
30				
31				
32				
33	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	__Page 17 ____
34				
35				
36	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	__Page 17 ____
37				
38				
39		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_ Not applicable in AFFIRM study__
40				
41				
42				
43				
44				
45				
46				
47				
48				
49				

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	__Pages 18-21__
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	__Not applicable__
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	__Pages 19-20__
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	__Pages 22-23__
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	__Page 23__
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	__Pages 22-23__

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	_DMC not required, explanation Pg 24__
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	__Pages 18, 25-26__
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	__Page 24__
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	__Page 13__

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	__Page 25__
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	__Page 25__
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	__Page 25__
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	__Not applicable__
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	__Page 20__
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	__Page 29__
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	__Page 27__
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	__Page 24__
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	__Page 27__
	31b	Authorship eligibility guidelines and any intended use of professional writers	__Page 28__
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	__Not applicable__

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_Not Applicable__
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_Not Applicable__

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](#)" license.

BMJ Open

Can Promoting Awareness of Fetal movements and Focussing Interventions Reduce Fetal Mortality? - A stepped wedge cluster randomised trial (AFFIRM)

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2016-014813.R2
Article Type:	Protocol
Date Submitted by the Author:	07-Feb-2017
Complete List of Authors:	<p>Heazell, Alexander; University of Manchester, Maternal and Fetal Health Research Centre</p> <p>Weir, Christopher; University of Edinburgh, MRC Hub for Trials Methodology Research; Edinburgh Clinical Trials Unit</p> <p>Stock, Sarah; Queen's Medical Research Institute, EH16 4TJ, Tommy's Centre for Maternal and Fetal Health, MRC Centre for Reproductive Health,; School of Women's and Infants' Health, University of Western Australia, Crawley WA 6009. (FMM)</p> <p>Calderwood, Catherine; The Scottish Government St Andrew's House, EH1 3DG., Chief Medical Officer for Scotland,</p> <p>CunninghamBurley, Sarah; University of Edinburgh, Public Health Sciences</p> <p>Froen, Frederik; Nasjonalt folkehelseinstitutt, Division of Epidemiology</p> <p>Geary, Michael; Rotunda Hospital, Parnell Square</p> <p>Hunter, Alyson; Royal Maternity Hospital, Grosvenor Road, BT12 6BB</p> <p>McAuliffe, Fionnuala; University College Dublin,</p> <p>Murdoch, Edile; Royal Infirmary of Edinburgh, NHS Lothian, EH16 4SA., Department of Neonatology</p> <p>Rodriguez, Aryelly; University of Edinburgh, (ECTU) Edinburgh Clinical Trials Unit</p> <p>Ross-Davie, Mary; NHS Education for Scotland, 3rd Floor, Hanover Buildings, 66 Rose Street, EH2 2NN.</p> <p>Scott, Janet; Sands, Victoria Charity Centre, Suite GF2 Ground Floor, 11 Belgrave Road, SW1V 1RB.</p> <p>Whyte, Sonia; Queen's Medical Research Institute, EH16 4TJ, Tommy's Centre for Maternal and Fetal Health, MRC Centre for Reproductive Health,</p> <p>Norman, Jane; , Queen's Medical Research Institute, EH16 4TJ</p>
Primary Subject Heading:	Obstetrics and gynaecology
Secondary Subject Heading:	Research methods
Keywords:	Reduced Fetal Movements, Perinatal Mortality, Stillbirth, Neonatal Death, Fetal Growth Restriction

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

1 Study Protocol

2 Can Promoting Awareness of Fetal movements and Focussing Interventions Reduce
3 Fetal Mortality? - A stepped wedge cluster randomised trial (AFFIRM)

4 Alexander E P HEAZELL,^{1,2} alexander.heazell@manchester.ac.uk

5 Christopher J WEIR,^{3,4} christopher.weir@ed.ac.uk

6 Sarah J E STOCK,^{5,6} sarah.stock@ed.ac.uk

7 Catherine J CALDERWOOD,⁷ catherine.calderwood@scotland.gsi.gov.uk

8 Sarah CUNNINGHAM-BURLEY,⁴ sarah.c.burley@ed.ac.uk

9 J Frederik FROEN,⁸ frederik.froen@fhi.no

10 Michael GEARY,⁹ mppgeary@gmail.com

11 Alyson HUNTER,¹⁰ alyson.hunter@belfasttrust.hscni.net

12 Fionnuala M MCAULIFFE,¹¹ fionnuala.mcauliffe@ucd.ie

13 Edile MURDOCH,¹² edile.murdoch@nhslothian.scot.nhs.uk

14 Aryelly RODRIGUEZ,^{3,4} aryelly.rodriguez@ed.ac.uk

15 Mary ROSS-DAVIE,¹³ mary.ross-davie@nes.scot.nhs.uk

16 Janet SCOTT¹⁴ janet.scott@uk-sands.org

17 Sonia WHYTE⁵ sonia.whyte@ed.ac.uk

18 Jane E NORMAN.⁵ jane.norman@ed.ac.uk

19

20 1. Maternal and Fetal Health Research Centre, Institute of Human Development,
21 University of Manchester. 2. St. Mary's Hospital, Central Manchester University
22 Hospitals NHS Foundation Trust, Manchester Academic Health Science Centre,
23 Manchester, M13 9WL. 3. Edinburgh Clinical Trials Unit, Edinburgh, UK 4. Centre for

24 Population Health Sciences, Usher Institute of Population Health Sciences and
25 Informatics, University of Edinburgh, Teviot Place, Edinburgh EH8 9AG. 5. Tommy's
26 Centre for Maternal and Fetal Health, MRC Centre for Reproductive Health, Queen's
27 Medical Research Institute, Edinburgh, EH16 4TJ.6. School of Women's and Infants'
28 Health, University of Western Australia, Crawley WA 6009. (FMM) 7. Chief Medical
29 Officer for Scotland, The Scottish Government St Andrew's House Edinburgh EH1
30 3DG. 8. Department of International Public Health, Norwegian Institute of Public
31 Health, PB 4404 Nydalen, N-0403 Oslo, Norway, 9. Rotunda Hospital, Parnell
32 Square, Dublin 1, Ireland. 10. Centre for Fetal Medicine, Royal Maternity Hospital,
33 Grosvenor Road, Belfast, BT12 6BB 11. UCD Obstetrics & Gynaecology, School of
34 Medicine, University College Dublin, Ireland. National Maternity Hospital, Dublin,
35 Ireland. 12. Department of Neonatology, Royal Infirmary of Edinburgh, NHS Lothian,
36 Edinburgh, EH16 4SA. 13. NHS Education for Scotland, 3rd Floor, Hanover
37 Buildings, 66 Rose Street, Edinburgh EH2 2NN. 14. Sands, Victoria Charity Centre,
38 Suite GF2 Ground Floor, 11 Belgrave Road, London, SW1V 1RB.

39

Abstract

Background - In 2013, the stillbirth rate in the UK was 4.2 per 1,000 live births, ranking 24th out of 49 high-income countries, with an annual rate of reduction of only 1.4% per year. The majority of stillbirths occur in normally formed infants, with (retrospective) evidence of placental insufficiency the commonest clinical finding. Maternal perception of reduced fetal movements (RFM) is associated with placental insufficiency and increased risk of subsequent stillbirth.

This study will test the hypothesis that the introduction of a package of care to increase women's awareness of the need for prompt reporting of RFM and standardised management to identify fetal compromise with timely delivery in confirmed cases, will reduce the rate of stillbirth. Following the introduction of a similar intervention in Norway the odds of stillbirth fell by 30%, but the efficacy of this intervention (and possible adverse effects and implications for service delivery) have not been tested in a randomised trial.

Methods - We describe a stepped wedge cluster trial design, in which participating hospitals in the UK and Ireland will be randomized to the timing of introduction of the care package. Outcomes (including the primary outcome of stillbirth) will be derived from detailed routinely collected maternity data, allowing us to robustly test our hypothesis. The degree of implementation of the intervention will be assessed in each site. A nested qualitative study will examine the acceptability of the intervention to women and health care providers and identify process issues including barriers to implementation.

Discussion - The data provided by this study will inform the management of women with RFM; which has been recurrently identified as suboptimal in cases of stillbirth. This will provide robust evidence to determine whether increased maternal awareness of RFM combined with a standardised management protocol to identify acute or chronic fetal compromise can reduce stillbirth.

67 *Trial Registration*

68 www.clinicaltrials.gov NCT01777022

69 *Version*

70 Protocol Version 4.2, 19th December 2016

71 *Keywords*

72 Reduced Fetal Movements; Perinatal Mortality; Stillbirth; Neonatal Death; Fetal
73 Growth Restriction.

74

75 **STRENGTHS AND LIMITATIONS OF THIS STUDY**

- 76 • This trial directly addresses the need for studies of the information given to
77 women regarding fetal movements and the subsequent management of reduced
78 fetal movements identified by Confidential Enquiries into Antepartum Stillbirths,
79 Systematic Reviews and the Stillbirth Priority Setting Partnership.
- 80 • A stepped-wedge cluster trial design in combination with routinely collected
81 maternity data allows the trial to be adequately powered to detect a difference in
82 stillbirth as a primary outcome.
- 83 • The pragmatic nature of the study represents the potential impact of the
84 introduction of such standardised care into clinical practice.
- 85 • The nested qualitative study will provide information regarding the acceptability
86 of the intervention and identify barriers and facilitators to its adoption.
- 87 • The lack of information on resource use before and throughout the study period
88 limits the ability to understand the consequences of the intervention on maternity
89 unit workload.

90

91

92 INTRODUCTION

93 *Stillbirth*

94 Stillbirth, defined in the UK as a baby with no signs of life after 24 weeks of completed
95 pregnancy ¹, remains the major cause of perinatal mortality in high-income
96 environments, with a recent series of papers in the Lancet on stillbirth issue calling for
97 renewed action in this area ². There is no single “cause” of stillbirth, and a significant
98 proportion of stillbirths remain unexplained, but fetal growth restriction, maternal
99 hypertension and low socioeconomic status are amongst the identifiable risk factors ³.
100 The concept that more can be done to reduce stillbirth in the UK and Ireland is
101 supported by data showing a marked variation in rates between resource rich
102 countries, when similar definitions of stillbirth are used ². Notably, the UK has a higher
103 rate than comparable resource rich countries such as Germany, Netherlands, New
104 Zealand and Norway with rates in the UK some 50% greater than those of the
105 Netherlands. Disappointingly, the annual rate of reduction in stillbirth from 2000 to
106 2014 in the UK was only 1.4% compared to 6.8% in the Netherlands and 2.8% in New
107 Zealand ². Rates of stillbirth in Scotland (3.7 per 1,000 births in 2014) and Ireland, at
108 (4.4 per 1,000 livebirths in 2013) are similar to rates in England and Wales at 4.2 per
109 1,000 livebirths (England and Wales, 2014) ⁴. The reduction of avoidable harm for
110 women and babies is viewed as a major priority for Government and its agencies
111 throughout the UK and Ireland. Consequently, several initiatives have been
112 developed by national governments in the UK and Ireland including the Scottish
113 Government Stillbirth Working Group, NHS England Saving Babies’ Lives Care
114 Bundle and the Welsh Assembly 1000 Lives Plus strategy. These strategies have
115 identified the need for better evidence to guide efforts to prevent stillbirths.
116 Using a robust priority setting strategy ⁵ the Lancet Stillbirth’s series steering
117 committee identified issues around detection and management of reduced fetal
118 movements (RFM) amongst the top ten key research questions on prevention and

1
2
3 119 management of stillbirth ⁶. This was confirmed in the UK-based Stillbirth Priority
4
5 120 Setting partnership involving over 1,700 parents and professionals which identified
6
7 121 two relevant issues among the highest ranked research questions regarding stillbirth:
8
9 122 i) which investigations identify a fetus at risk of stillbirth after a mother believes she
10
11 123 has experienced reduced fetal movements? and ii) would more accessible evidence-
12
13 124 based information on signs and symptoms of stillbirth risk, designed to empower
14
15 125 women to raise concerns with healthcare professionals, reduce the incidence of
16
17 126 stillbirth? ⁷ Thus, RFM has been identified as a highly-relevant area of study by
18
19 127 parents, professionals and researchers.
20
21 128

22
23 129 *Reduced Fetal Movements, Stillbirth and Placental Insufficiency*
24

25
26 130 There is a clear association between maternal perception of RFM and late stillbirth
27
28 131 dating back over four decades ⁸. In a recent series of 2,000 women, the adjusted OR
29
30 132 (95% CI) of late stillbirth in women with RFM (compared with controls) was 2.37
31
32 133 (1.29-4.35) ⁹. One international study of 1,714 women who experienced a stillbirth
33
34 134 found that 30% had noted significant RFM prior to the diagnosis of stillbirth ¹⁰.
35
36 135 Although the mechanisms have not been fully delineated, it is likely that RFM and
37
38 136 stillbirth are linked by a common pathology, that of placental dysfunction ¹¹. There is
39
40 137 good evidence linking placental dysfunction and RFM. Compared to controls with an
41
42 138 active fetus women who have fewer fetal movements on ultrasound scan immediately
43
44 139 prior to caesarean section are more likely to have umbilical cord gas measurements
45
46 140 indicative of acidaemia, hypoxaemia, and hypercapnia ¹². Women delivering within
47
48 141 one week of an episode of RFM show differences in placental structure and function
49
50 142 which are reminiscent of those seen in fetal growth restriction (FGR) and stillbirth ^{13 14}.
51
52 143 Additionally, the odds of fetal growth restriction (FGR, defined as being at less than
53
54 144 the 10th centile for gestation adjusted birthweight) were greater in women with RFM
55
56 145 compared with controls (adjusted OR 1.6, 95% CI 1.1–2.2 ¹⁵). Taken together these
57
58
59
60

data are strong evidence that placental dysfunction is associated with RFM, and a causative pathway seems likely.

The evidence linking placental dysfunction and stillbirth is even stronger; a systematic review of placental pathology in stillbirths described abnormalities in up to 65% of cases¹⁰. Amongst the 291 stillbirths in Scotland in 2010, 137 (47%) had evidence of placental dysfunction¹⁶. Given that the placenta was examined in only 80% of stillbirths, the true prevalence of placental dysfunction is likely to be higher. In addition, between 20%-40% of stillborn babies are reported to have FGR, as defined by a birthweight less than the 10th centile¹⁷. Additionally, the Lancet report notes that “placental pathologies accounted for one in four deaths across all gestational ages, and were contributory or causal in more than half of cases”⁶. Given that stillbirth is strongly related to placental dysfunction, and RFM is a “biomarker” of placental dysfunction then better management of women presenting with RFM focussing on the detection of placental dysfunction might reduce the risk of stillbirth.

Formal Fetal Movement Counting

Although prenatal detection of FGR is improved by fetal movement counting¹⁸, a systematic review¹⁹, and a large and influential cluster randomised trial (which dominates the systematic review) showed that routine fetal movement counting using the count to ten charts had no effect on perinatal mortality²⁰. Thus, the National Institute for Health and Social Care Excellence (NICE) recommended that “Routine formal fetal movement counting should not be offered”²¹. Importantly, the large cluster randomised trial tested a specific alarm limit for RFM, but did not recommend a specific management strategy for women who did present with RFM. There were two important observations from this study, firstly that in both groups the perinatal mortality rate was lower than contemporary or subsequent periods in the UK and secondly that more women in the fetal movement counting arm came in with a live baby who subsequently died compared with the control arm (19 vs 11), suggesting

174 that one reason the strategy failed to reduce perinatal mortality was inadequate
175 investigation and management of those presenting with RFM ²⁰.

176
177 *Optimal strategy for determining RFM to prompt maternal presentation to the*
178 *maternity service*

179 Maternal concern about RFM is a common reason to contact maternity services with
180 between 6-15% of women presenting during the third trimester.^{22 23} Nevertheless,
181 delays in reporting RFM to maternity care providers may increase the risk of adverse
182 outcome.^{24 25} The lack of good-quality information given to women about fetal
183 movements has been highlighted as an example of suboptimal care in Confidential
184 Enquiries into Antepartum Stillbirth.^{26 27} Qualitative studies suggest that women
185 frequently perceive RFM two days prior to the diagnosis of fetal death, and in some
186 cases contractions were misinterpreted as fetal movements.²⁸ Therefore, giving
187 information to women regarding fetal movements and when they should be
188 concerned about RFM is a key component of an intervention to reduce stillbirth.

189 However, giving clear information about RFM can be challenging as there is no
190 uniform threshold of fetal movements below which perinatal morbidity increases ²³,
191 and no evidence that a specific threshold performs better than maternal perception of
192 reduced fetal movements alone ⁸. Current guidelines from the RCOG and PSANZ ²⁹
193 ³⁰, informed by a large Norwegian study ³¹ suggest that it is maternal *perception* of
194 decreased fetal movement which is important. Therefore, information for pregnant
195 women in this study (shown in Supplementary File 1) described the importance of
196 fetal movements, the need to get to know normal fetal activity, how fetal movements
197 change in late pregnancy and who to contact if the mother perceives RFM. The
198 educational package aimed to ensure that these messages were reinforced by staff
199 behaviour at antenatal contacts.

200
201 *Optimal strategy for investigation and management of women presenting with RFM.*

1
2
3 202 A recent systematic review found there are no proven strategies for the investigation
4
5 203 and management of women presenting with RFM ³². Cardiotocography (CTG) is
6
7 204 routinely used to ascertain fetal wellbeing, and it is the cornerstone of the RCOG
8
9 205 guideline ³⁰. However, data from Norway, suggests that ultrasound assessment of
10
11 206 fetal size is often the most helpful investigation, performing well on both an absolute
12
13 207 basis, and compared with other interventions ³³. In a series of over 3,000 women with
14
15 208 RFM, ultrasound (including measurement of fetal biometry and liquor volume) was
16
17 209 found to be useful in detecting abnormalities in 11.6% of scans. In 71% of women in
18
19 210 whom an abnormality was found, ultrasound was the only technique that detected an
20
21 211 abnormality. Additionally, 85% of abnormalities detected by ultrasound, were
22
23 212 important in informing the clinical management of the woman ³³. These data are
24
25 213 supported by a smaller UK study which found that abnormalities detected on CTG or
26
27 214 ultrasound scan were most strongly associated with adverse outcome in women with
28
29 215 RFM, with identification of abnormal estimated fetal growth centile on scan being the
30
31 216 test most highly predictive of poor outcome ³⁴. Perhaps this is not surprising, given the
32
33 217 strong association between RFM and placental dysfunction and the central
34
35 218 importance of ultrasound in the identification and management of small for gestational
36
37 219 age babies ³⁵. Given these data, it is concerning that a survey of clinicians in Scotland
38
39 220 showed that fewer than 5% would routinely refer women with RFM for ultrasound
40
41 221 examination (unpublished data from June 2012), and a survey of 223 UK midwives
42
43 222 and obstetricians described that 17.9% of respondents would perform an ultrasound
44
45 223 scan ³⁶. These views of clinicians may reflect the variable quality of local guidelines,
46
47 224 which are frequently not based on national recommendations, even those for which
48
49 225 there is strong evidence ³⁷. The variation in information given to women and
50
51 226 subsequent management of RFM has been highlighted as sources of suboptimal care
52
53 227 in two confidential enquiries into antepartum stillbirth ^{26 27}. Therefore, we believe that
54
55 228 current investigation of women presenting with RFM is inadequate, hence using the
56
57 229 best available evidence, we have drafted what we consider to be a robust evaluation
58
59
60

230 protocol for investigation of women with RFM.

231 *Potentially efficacy of a package of intervention for RFM*

232 Supportive data for the package of interventions used in this study (information for

233 women and standardised management protocol) comes from a large observational

234 “clinical quality improvement study” in Norway which found a significant fall in rates of

235 stillbirth (from 3.0/1,000 to 2.0/1,000 [OR 0.67 95% CI 0.48–0.93]) after the

236 introduction of an intervention package consisting of written information for women

237 about awareness of RFM combined with consensus guidelines for health

238 professionals about their management ³¹. Although this study was not randomised,

239 and therefore constitutes only level II-3 evidence, it has informed recommendations

240 from the Royal College of Obstetricians and Gynaecologists (RCOG) and Perinatal

241 Society of Australia and New Zealand (PSANZ) that “women should be advised to be

242 aware of their baby’s individual pattern of movements and that if they are concerned

243 about a reduction in or cessation of fetal movementsthey should contact their

244 maternity unit” ^{29 30}. Following initial publication of the Norwegian study, a re-analysis

245 was required as discrepancies between stillbirth rates in the study and the Medical

246 Birth Registry of Norway were identified. This reanalysis found the reduction in

247 stillbirth rates was of borderline statistical significance (OR 0.72, 95% CI 0.50-1.03).

248 The authors concluded that further studies were needed to determine whether this

249 approach was associated with a reduction in stillbirth ³⁸.

250 Importantly, in the Norwegian study, there was no increase in the proportion of

251 women who presented with RFM when rates were compared before and after the

252 intervention ³¹. However, women with RFM presented significantly earlier to hospital

253 than they had hitherto, potentially allowing time for intervention to reduce perinatal

254 mortality. These data suggest that a package of interventions encouraging women

255 with RFM to present early to hospital, combined with a structured approach to their

256 management might reduce rates of stillbirth without contributing to a large increase in

257 admissions antenatally.

258

259 *Potential harms of a package of care around increased awareness and optimised*
260 *management of RFM*

261 Any clinical intervention which aims to improve outcomes also has the ability to do
262 harm. Thus, it is essential that the intervention proposed is rigorously evaluated using
263 the gold standard technique of a randomised trial, rather than being introduced as a
264 service development. When the study began, there was a small window of
265 opportunity to do this, as the enthusiasm to improve current management of RFM is
266 such that routine introduction of the package of care is unlikely to be delayed much
267 further than the current scheduled end date of this study. Possible harms of a
268 package of care consisting of a management plan for identification and delivery of the
269 “at risk” fetus, together with strategies for increasing pregnant women’s awareness of
270 the need to report early include increased maternal anxiety and increased
271 intervention (including hospital admission, induction of labour and Caesarean section)
272 which itself is associated with pregnancy related complications. The available
273 evidence is reassuring on some of these issues. A systematic review of 23
274 publications from 16 studies found three studies involving 2,030 women addressing
275 maternal concern and an additional three studies involving 1,468 women investigating
276 maternal-fetal attachment. These demonstrated no evidence of increased maternal
277 anxiety and results regarding maternal-fetal attachment were discordant.³⁹ In the
278 Norwegian service development study, the package of care increased rates of follow
279 up of women, but there was no increase in admissions overall, admissions for
280 induction or admissions for emergency caesarean section ³¹ – again, whilst
281 reassuring these outcomes require formal evaluation in a randomised and relevant
282 setting to the UK and Republic of Ireland. The final possible harm of the package is
283 around increased resource use, and the opportunity cost of focussing on RFM rather
284 than other potential methods to prevent stillbirth.

285

286 **RATIONALE**

287 The aim of this study is to test the hypothesis that a package of interventions
288 consisting of strategies for increasing pregnant women’s awareness of the need to
289 report early when they perceive a reduction in fetal movements, followed with a
290 management plan for identification and delivery of the “at risk” fetus in such women,
291 will reduce rates of stillbirth.

292

293 **STUDY OBJECTIVES**

294 *Primary Objective*

295 The primary objective is to answer the research question ‘Does the introduction of a
296 protocol for detection and management of decreased fetal movements reduce rates
297 of stillbirth?’ The secondary objectives are to answer the following research
298 questions:

- 299 • What is the effect of the intervention on rates of caesarean section and induction
300 of labour?
- 301 • What is the effect of the intervention on rates of admission to the neonatal
302 intensive care unit?
- 303 • What is the effect of the intervention on the proportion of women with FGR
304 remaining undelivered by 40 weeks gestation?
- 305 • What is the acceptability of such a package of care to pregnant women and their
306 health care providers?
- 307 • What other process outcomes are influenced by the intervention, such as health
308 care provider/patient interactions?

309

310 ENDPOINTS

311 *Primary Outcome*

312 The primary endpoint is stillbirth (antepartum and intrapartum). We will use the UK
313 definition of stillbirth which is “a baby delivered without signs of life after 23⁺⁶ weeks”
314 ⁴. Where gestation is uncertain we will include all babies with a birth weight of 500g
315 or more.

316 *Secondary Endpoints*

317 Other measures of perinatal mortality including:

- 318 • Stillbirth at 37 weeks gestation and above
- 319 • Stillbirth at 28 weeks gestation and above (WHO definition of stillbirth)
- 320 • Stillbirth at 22 weeks gestation and above (international stillbirth alliance
321 definition)
- 322 • Stillbirths amongst normally formed infants of 22 weeks gestation and above,
323 24 weeks gestation and above, 28 weeks gestation and above and 37 weeks
324 gestation and above.
- 325 • Perinatal mortality (defined as stillbirth at 24 weeks gestation and above and
326 deaths in the first seven days of life)
- 327 • Rates of caesarean section
- 328 • Rates of induction of labour (for any indication)
- 329 • Rates of elective delivery (induction of labour and caesarean section prior to
330 the onset of labour) overall
- 331 • Rates of induction of labour at 39 weeks gestation or later
- 332 • Mean gestation at induction of labour
- 333 • Rates of admission to the neonatal unit (and their reasons)

- 334 • Rates of admission to the neonatal unit for more than 48 hours
- 335 • Rates of admission to the neonatal unit for term babies (those born at 37
- 336 weeks 0 days or greater)
- 337 • Proportion of infants with fetal growth restriction (less than the 5th centile,
- 338 customised for gender) remaining undelivered at or after 40 weeks gestation
- 339 • Birthweight centile (according to the Intergrowth birthweight centile calculator
- 340 at <https://intergrowth21.tghn.org>)
- 341 • Rates of spontaneous vaginal delivery
- 342 Other secondary outcomes are the baby parameters:
- 343 • Gestation at birth
- 344 • Proportion of babies born preterm (<37 weeks gestation)
- 345 • Gender of the baby
- 346 • Birthweight of the baby
- 347 • Apgar score at 5 minutes
- 348 • Proportion of babies with 5 minute Apgar score < 7
- 349 • Proportion of babies with 5 minute Apgar score < 4
- 350 • Resuscitation required at birth

351 We will also collect the following data: maternal age, maternity unit of delivery,
352 birthweight, gestation of delivery, parity, gestation, sex, smoking (current and ever),
353 maternal body mass index (BMI), number of babies (one or more), ethnicity (to allow
354 a customised birthweight centile to be generated), method of delivery, deprivation
355 category (where available) and other neonatal variables including Apgar score and
356 encephalopathy. Adjustment will be made for the following variables: (maternal age,

maternity unit of delivery, parity, smoking status, maternal BMI, number of babies
[one or more] and ethnicity)

359

360 STUDY DESIGN

361 This is a multicentre, stepped wedge cluster randomised trial of a package of care
362 consisting of a management plan for identification and delivery of the 'at risk' fetus,
363 together with strategies for increasing pregnant women's awareness of the need to
364 report RFM early. The trial developed from a planned quality improvement project
365 proposed by the Scottish Government to reduce stillbirths. This was planned to
366 emphasise the importance of fetal movement monitoring and was to be rolled out to
367 all NHS maternity units in Scotland. However, prior to this change it was agreed that
368 the roll out could be performed in such a way as to allow the assessment of the effect
369 of the intervention, the stepped-wedge design would be the natural choice in this
370 circumstance.

371 The study will take place in participating hospitals in the UK and Ireland (a complete
372 list is available <http://www.crh.ed.ac.uk/affirm/randomised-hospitals/>). A nested
373 qualitative study will examine the acceptability of the intervention to patients and
374 health care providers and identify process issues (barriers to implementation).
375 Clinical audit (detailed in Appendix 3) conducted after the change in practice will be
376 used to determine the effect of interventions on process outcomes (e.g. number of
377 women presenting with reduced fetal movements, interval between perceiving
378 reduced fetal movements and presentation to hospital, number of ultrasound scans,
379 number of admissions for induction of labour). A diagram indicating randomisation of
380 hospital groupings in the stepped wedge design is shown in Figure 1.

381 The interventions will be introduced over a 32 month period. Data will be collected
382 over a 36 month period. Data in the 'active phase' after introduction of the

intervention will be compared to data in the ‘control phase’ – the period during which usual care processes in study sites are followed from study start to the time of introduction of the intervention. Given that it will take individual units some time (a) to effect change in management in their unit from time of introduction of the intervention and (b) that it will take some time for this change in practice to impact on clinical outcomes, we plan a “washout” period of two months after the introduction of the intervention during which data will not be included in either group for analysis (Figure 1). Data will be collected four months after the last birth, a further two months has been included for data analysis, giving a total study duration of 42 months.

STUDY POPULATION

Number of participants

Participants will be those delivering at all the sites over the study period (36 months). All eligible women will be recruited to the cluster randomised controlled trial. Based on previous delivery numbers, after accounting for a washout period of two months (and assuming no withdrawals or losses to follow up) this is estimated to be a total of around 143,140 women per annum. A subset of around 30 participating women and 30 midwives, sonographers and obstetricians will be recruited to the nested qualitative study, which is based in the Scottish sites.

Inclusion criteria

We will include all women delivering at one of the participating maternity units for the duration of the study. Women who have been seen at any of the maternity units but who deliver at home will not be included. The duration of the study will be 42 months from the start of the trial (01/02/2014). For practical reasons, participants for the nested qualitative study will be recruited from the participating units in Scotland.

Exclusion criteria

409 We will exclude women as follows:

- 410 • Women for whom data on delivery outcomes is still unavailable four months after
- 411 the date of delivery
- 412 • Women delivering in the “washout” period in each unit.

413 Members of the trial management group and participants who do not
414 speak/understand English will be excluded from participating in the nested qualitative
415 study.

416 *Identifying participants*

417 Women will be identified from those whose data is included in routine data returns
418 from each unit. Potential participants for the nested qualitative study will be identified
419 from those attending antenatal clinics in participating hospitals, and/or local staff.

420 *Consenting participants*

421 The main study is a stepped wedge cluster randomised trial of a package of care
422 which would be introduced in many of the participating units regardless of whether
423 the trial was on-going or not and the trial uses only routinely collected data on
424 participants. The ethics committee indicated that formal individual patient consent is
425 not necessary for the main trial. Participants in the nested qualitative study will be
426 asked for individual consent.

427 *Screening for eligibility*

428 As participants are not directly recruited we will not perform any specific screening
429 tests for this aspect of this project. Participants for the nested qualitative study will
430 be: (i) Pregnant women attending hospitals who are participating in the main trial in
431 Scotland. Purposive sampling will ensure that the final sample set includes women
432 who have and who have not experienced RFM, both before and after the introduction
433 of the intervention; (ii) Hospital staff (including midwives, ultrasonographers and

434 obstetricians/radiologists) working in participating hospitals in Scotland. There will be
435 no specific screening tests for eligibility for the nested qualitative study, except that
436 women who have experienced a stillbirth in the index pregnancy will not be
437 approached.

438 *Ineligible and non-recruited participants*

439 Potential participants for the nested qualitative study who are not approached or who
440 decline will have no specific interventions / procedures.

441 *Withdrawal of Study Participants*

442 The nature of a cluster randomised study is such that it is not possible for the
443 participant to withdraw from the “cluster” unless she changes maternity unit part way
444 through her pregnancy. We plan to collect routinely recorded anonymised data;
445 patients have the right to opt out of having their data used – if this happens their data
446 would be excluded from the study database (e.g. under the Confidentiality and
447 Security advisory Group Report 2002 and the Data Protection Act (1998)
448 requirements for fair processing of data). Participants in the nested qualitative study
449 who wish to withdraw will be allowed to do so. Their data will be retained and used,
450 unless they additionally indicate that they wish to withdraw their data.

451 **RANDOMISATION**

452 *Randomisation Procedures*

453 This is a cluster-randomised, stepped-wedge design trial wherein maternity units
454 rather than individual patients are randomised. All units will implement the fetal
455 movement monitoring intervention at some point during the trial; the random element
456 is the time point at which this will occur, the so-called “step” of the stepped-wedge
457 design. Participating maternity units will be blinded to their randomly allocated time
458 point until the time this is required to be revealed to enable the necessary training in
459 the implementation of the intervention to be delivered. Primary and secondary

outcomes of the trial will be gathered in a blinded manner via routinely collected data sources.

Maternity units which are in close proximity to each other will be grouped for the purposes of randomisation. This will assist with the feasibility of delivering the training for and implementation of the intervention. Furthermore, this local synchronisation of the intervention implementation will minimise the chances of contamination (introduction of the intervention prematurely) from maternity units which have already implemented the intervention to those not yet randomised.

The order in which the groups of maternity units step in to implement the intervention will be determined by computer generated random numbers from a uniform distribution. The randomisation list will be held by the Edinburgh Clinical Trials Unit (ECTU). The identities of the research team staff whose roles in the trial require them to be unblinded to randomisation codes will be recorded in the trial master file (TMF).

Treatment Allocation

Participating sites will be randomised to different schedules for implementing the intervention. All units will be providing conventional treatment at baseline according to local practice – this is the treatment established before the study starts. Sites will be randomised to “active” treatment in turn as described above. Active treatment will consist of a package of care consisting of a management plan for identification and delivery of the ‘at risk’ fetus, together with strategies for increasing pregnant women’s awareness of the need to report RFM early. The recommended management plan for identification and delivery of the “at risk” fetus is shown in Figure 2. Practice change in the active units will be achieved by: (i) written/email information to all clinicians (doctors, midwives and ultrasonographers) in each unit about the study protocol and amendment of the local protocol for Reduced Fetal Movements (RFM) to that of the study protocol; (ii) a short web-based training package taking approximately one hour to complete for all clinicians in each centre and (iii) training /information sessions to

run in each unit and (iv) posters in each unit to describe the practice change. Strategies for encouraging clinicians to increase pregnant women's awareness of fetal movement will include all the above and also a fetal movement leaflet for pregnant women (shown in Supplementary Information 1). The Norwegian quality improvement study showed inconclusive results regarding the effect of the intervention in non-European women.⁴⁰ To attempt to address this, the AFFIRM information leaflet was available in 12 languages including: Arabic, Bengali, English, Hindi, Hungarian, Latvian, Lithuanian, Mandarin, Polish, Russian and Urdu. Furthermore, by including staff education which highlighted the need to ask women about fetal movements in routine antenatal consultations as many women as possible should have received information about what to do if they perceive RFM.

Once units have begun active treatment it is not anticipated that they will return to conventional treatment. We will conduct an audit of women presenting with reduced fetal movements and assess the proportion of staff completing the online training to assess the extent to which sites have followed the intervention plan. Units will be informed about treatment allocation as near as possible to the implementation of the "active" treatment. For practical purposes, we anticipate that each unit will need around three months' notice before the "active" treatment is introduced, hence units will be informed of the timing of their treatment allocation (step) three months before the active treatment is due to start. The treatment allocation will not be administered blind and there are no restrictions on concomitant care or other interventions during the study, hence there is no need for emergency unblinding and there are no stopping rules for the study.

510

511 **DATA COLLECTION**

512 For the main trial, data will be accessed from the information routinely collected
513 during the clinical management of the patient. For consistency, we will normally only

1
2
3 514 include data items which become available within four months after the delivery date
4
5 515 in question, although we may seek advice from the independently-chaired trial
6
7 516 steering committee (TSC) about exceptions as they arise. Different data sources will
8
9 517 be used for different regions of the study: (i) In Scotland the source data will be
10
11 518 SMR2 and the Scottish Birth record, (ii) In Ireland the source data will be the National
12
13 519 Perinatal Reporting System (NRPS http://www.esri.ie/health_information/nprs), (iii) In
14
15 520 Northern Ireland, the source data will be the Northern Ireland maternity Statistics
16
17 521 database (NIMATS), (iv) In England and Wales, the source data will be the ONS, or
18
19 522 other relevant body. Data will be collected retrospectively on an annual basis from all
20
21 523 sources. We will assume that data unavailable four months after the woman
22
23 524 delivered is likely to be unobtainable (but see note in Study Design section above).
24
25 525 Thus, data on the first year of the study will be collected at month 16; data on the
26
27 526 second year will be collected at month 28 etc.
28
29
30 527 Data are routinely collected. A formal request for data access will be made at the
31
32 528 start of the study. This will require (i) in Scotland – Privacy Advisory Committee
33
34 529 approval and a formal approach to NHS Scotland Information Services Division (ISD)
35
36 530 (ii) in Ireland a formal approach to NRPS (iii) NIMATS in Northern Ireland (iv) in
37
38 531 England and Wales a formal approach will be made to the relevant bodies.
39
40
41 532 Data will then be sent to the electronic Data Research and Innovation Service
42
43 533 (eDRIS) National Safe Haven (NHS National Services Scotland) by secure file
44
45 534 transfer protocol (or other similar) for storage and subsequent analysis within a
46
47 535 secure project area (dedicated to the AFFIRM study). Further information on the
48
49 536 National Safe Haven is available at [http://www.isdscotland.org/Products-and-](http://www.isdscotland.org/Products-and-Services/eDRIS/Becoming-an-eDRIS-User/#NSS-National-Safe-Haven)
50
51 537 [Services/eDRIS/Becoming-an-eDRIS-User/#NSS-National-Safe-Haven](http://www.isdscotland.org/Products-and-Services/eDRIS/Becoming-an-eDRIS-User/#NSS-National-Safe-Haven). Briefly, the
52
53 538 National Safe Haven is located on a secure server, in which trusted and authorised
54
55 539 researchers can analyse individual level data while maintaining the utmost
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

540 confidentiality. It is anticipated that all study analysis will be done within the Safe
541 Haven, using one of the available statistical packages (e.g. R, SPSS).

542 Identifiers on Scottish data within the National Safe Haven are concealed from
543 researchers. Data from outwith Scotland will be anonymised before submission to the
544 National Safe Haven. We propose that data submitted to the National Safe Haven
545 will be “anonymised” by the data provider. However, we propose that the
546 anonymisation link will be retained at the source so that it will be possible to re-link
547 data retrospectively. The rationale for retaining the ability of local data guardians to
548 re-link data is because it is important to retain the possibility of identifying individual
549 patients retrospectively. Examples include: (i) It is possible that some additional
550 important data may be available at a late stage on individual participants – e.g. in the
551 scenario where the woman or baby had a major adverse event and spent a long time
552 in hospital before discharge or death and (ii) Although our protocol and outcome
553 analysis does not require identifiable data, we believe this will be a ‘once in a lifetime’
554 study, and that subsequent secondary analyses could yield important information for
555 patients and for policy makers. If retrospective identification is not possible, this will
556 limit further analysis. One likely example of future analyses is to determine the effect
557 of the intervention on different causes of stillbirth. This is outwith the scope of the
558 current protocol, but could be done relatively straightforwardly, by linking nationally
559 recorded information on “cause” of stillbirth to our study database. We anticipate that
560 such additional analyses would require additional ethics approval, but without a
561 process by which to re-link data, it will not be possible to perform such subsequent
562 analyses.

563 All Investigators and study site staff involved with this study will comply with the
564 requirements of the Data Protection Act 1998 (or equivalent for those outwith the UK)
565 with regard to the collection, storage, processing and disclosure of personal

information and will uphold the Act's core principles. Published results will not contain any personal data that could allow identification of an individual participant.

In addition to the data recorded above, all sites will be asked to provide a copy of their guidelines around (i) maternal awareness of RFM and (ii) management of women presenting with RFM. Copies of guidelines will be sought by the study office (a) at the start of the study (b) immediately before initiation of the intervention in each specific unit and (c) six months after initiation of the intervention in each specific unit.

For the nested qualitative study, we will perform interviews of healthcare workers and a small nested cohort of pregnant women about their experiences of fetal movement and of this intervention. We shall ensure a diversity of age and include nulliparous and multiparous women (n=30 in total). Ten interviews will be conducted with each of the following groups of health care providers: obstetricians, midwives and sonographers/radiologists. The interviews will take a semi-structured format (sensitising and piloting interviews will be conducted prior to the commencement of the trial and in the first month of the nested qualitative study). This format will ensure the same categories of data will be obtained from each participant but also allow individual responses to be fully explored.

583

584 **STATISTICS AND DATA ANALYSIS**

585 *Sample size calculation*

The sample size is the number of women delivering in hospitals participating in the study. This was initially planned to include sites in Scotland, totalling around 58,000 deliveries per year with 16 consultant led maternity units, 20 smaller units each delivering less than 350 babies per year, and seven units delivering less than five births per year. The units involved in Perinatal Ireland (an all-Ireland research consortium across 7 academic sites in Ireland currently funded by the Health

Research Board, Ireland) have 50,000 births per year with seven large sites. Combining one or two of the smaller units and one larger unit into a single “hospital group” for each local area could provide 24 hospital “groups” – the details of hospital groupings will be reviewed and finalised immediately prior to randomisation. In total, 36 sites expressed interest in participating in the study, although 2 were unable to participate in the study and withdrew before randomisation. In total, 34 units were randomised, these were situated throughout the UK and Ireland (10 in England, 4 in Ireland, 15 in Scotland and 5 in Wales) with 143,140 births per annum.

We calculated statistical power using the methodology for stepped wedge designs proposed in Hussey and Hughes (2007).⁴¹ First, we analysed stillbirth event data from the Scottish Perinatal and Infant Mortality and Morbidity Report (SPIMMR) covering years 2005-2010¹⁶ to determine estimates of between- and within-unit variability in stillbirth rate. Analysis was by generalized linear mixed model for binary outcomes. The power calculation, as per equations (#7) and (#8) in⁴¹ assumed: significance level 5%; analysis by generalized linear mixed model; deliveries equally distributed across hospital groupings; baseline stillbirth rate 0.438%¹⁶; cluster coefficient of variation 0.333.

Finally, the statistical power depends on the number of groups in which the intervention is implemented at each stage of the stepped wedge design and the duration of recruitment at each “step”. Our study design proposes sequential introduction of the intervention into three hospital groups at a time in eight steps at four month intervals. This would give 92.4% power to detect a 30% risk reduction under the intervention and 80.7% power to detect a 25% reduction. A 30% risk reduction was seen in the Norwegian study; the anticipated effect sizes of 25% and 30% relative reduction take into account that the intervention will not have the power to reduce all stillbirths, since 20% of stillbirths in Ireland⁴² and 15% in Scotland¹⁶ are associated with congenital anomaly.

1
2
3 619 The power actually achieved in the study will be slightly lower, as deliveries during
4
5 620 the two month “transition” period following implementation of the intervention in a site
6
7 621 will not be included in the analysis. The effect of this was explored using the Stata
8
9 622 function steppedwedge,⁴³ which showed the statistical power would become 88.2%
10
11 623 (30% risk reduction) and 74.6% (25% risk reduction). It is anticipated that
12
13 624 unavailability of data and women asking to withdraw their data will be less than 1%.

14
15 625 *Proposed analyses*

16
17
18 626 For the binary primary and secondary outcomes, data will be analysed by
19
20 627 generalized linear mixed model with a random effect for hospital and fixed effects for
21
22 628 the intervention implementation and study time period. A site by intervention
23
24 629 interaction random effect will be included in the model and retained if it explains an
25
26 630 important proportion of the variability in outcomes. The primary analysis of data will
27
28 631 be on an intention to treat basis (the design of the trial means it is not possible to
29
30 632 determine individual patient /caregiver compliance with the intervention). An “on
31
32 633 treatment” variable will be calculated for which women will be grouped as active or
33
34 634 control according to when the intervention was actually implemented in their site,
35
36 635 instead of when the site was randomised to implement the intervention. The primary
37
38 636 outcome will be reanalysed in two sensitivity analyses. Firstly, we will perform the
39
40 637 analysis according to the actual timing of the implementation of the intervention
41
42 638 rather than the randomised timing of the intervention using the “on treatment”
43
44 639 classification. Secondly, we will perform the analysis in the subgroup of sites who
45
46 640 were deemed to have implemented the intervention effectively according to the
47
48 641 perception of the Principal Investigator at each site. The accuracy of this perception
49
50 642 will be confirmed with the findings of a site audit (details in Appendix 3). There will be
51
52 643 no attempt to correlate the impact of the intervention according to the results of the
53
54 644 site audit.

There are no planned imputations for missing data. However, if the missing data rate for smoking status during pregnancy is relatively high an imputation technique will be devised. The imputation method will be informed using smoking history at booking and age at delivery ⁴⁴. A pre-specified subgroup analysis will be performed for babies with and without congenital anomalies, and will be implemented by testing for an intervention by congenital anomaly interaction added to the generalised linear mixed model described above. No formal interim analyses for efficacy or safety will be performed. A full statistical analysis plan will be finalised prior to locking of the study database.

Qualitative Data

For the nested qualitative study, the data will be audio recorded and transcribed. The data will be coded thematically and an analytical framework developed to make sense of patient experience of fetal movement and the intervention and also health care providers' perspectives and experiences. NVivo will be utilised to support the analysis.

Process outcomes

The process outcomes being assessed by the (rates of induction of labour, number of women presenting with reduced fetal movements, interval between perceiving fetal movements and presenting to hospital) will be analysed using the same methods as for the main trial, with the exception of the continuous outcome (interval between perceiving fetal movements and presenting to hospital) which will be analysed using a normal linear mixed model.

ADVERSE EVENTS

This is not a Clinical Trial of an Investigational Medicinal Product (CTIMP) so adverse events will not be formally reported. Stillbirth and other measures of fetal and

maternal morbidity are outcomes of the study. The purpose of the intervention is to reduce such adverse events. Therefore, due to the low risks for this trial, a separate DMC is not required and the Trial Steering Committee (TSC) will cover any responsibilities normally allocated to a DMC. If considered necessary, the TSC may review unblinded data for the study, including morbidity and mortality indices. No other adverse event reporting will be undertaken.

677

678 TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

The trial will be coordinated by a Project Management Group, consisting of the grant holders and the Trial Manager. The Chief Investigator (JN) will lead the project management group. The Trial Manager will oversee the study and will be accountable to the Chief Investigator. A TSC will be established to oversee the conduct and progress of the trial. The terms of reference and a draft template for reporting will be ratified in one of the early meetings of the TSC.

Investigators and institutions involved in the study will permit trial related monitoring and audits on behalf of the co-sponsors (ACCORD: Academic and Clinical Central Office for Research & Development - Joint office for University of Edinburgh and NHS Lothian, Sponsor contact: ray.french@ed.ac.uk), research ethics committee (REC) review, and regulatory inspection(s). In the event of an audit or monitoring, the Investigator agrees to allow the representatives of the sponsor direct access to all study records and source documentation. In the event of regulatory inspection, the Investigator agrees to allow inspectors direct access to all study records and source documentation.

694

695

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

696 *Study monitoring and audit*

697 The sponsor determined that as no individual participants were recruited to the
698 intervention, and it was not a clinical trial of an investigational medicinal product
699 (CTIMP) no formal monitoring and audit was required.

700

701 *Good Clinical Practice and Ethical Conduct*

702 The study will be conducted in accordance with the principles of the research
703 governance framework operational and good clinical practice in the relevant country.

704 A favorable ethical opinion has been obtained from the Scotland A REC (Reference
705 13/SS/0001) and local research and development approval has been obtained prior
706 to commencement of the study.

707 Local study investigator(s) will be appointed to each site (or for small units, groups of
708 sites). S/he will be responsible for the overall conduct of the study at the site and
709 compliance with the protocol and any protocol amendments.

710

711 **STUDY CONDUCT RESPONSIBILITIES**

712 *Protocol amendments*

713 Any changes in research activity, except those necessary to remove an apparent,
714 immediate hazard to the participant in the case of an urgent safety measure, will be
715 reviewed and approved by the Chief Investigator and Sponsor. Amendments to the
716 protocol will be submitted in writing to the appropriate REC and local Research and
717 Development (R&D) department for approval prior to participants being enrolled into
718 an amended protocol.

719

720 *Protocol violations and deviations*

721 Investigators will not implement any deviation from the protocol without agreement
722 from the Chief Investigator and appropriate REC and R&D department approval
723 except where necessary to eliminate an immediate hazard to trial participants. In the
724 event that an Investigator needs to deviate from the protocol, the nature of and
725 reasons for the deviation will be recorded. If this necessitates a subsequent protocol
726 amendment, this will be submitted to the REC, and local R&D department for review
727 and approval if appropriate.

728 *Serious breach requirements*

729 A serious breach is one which is likely to effect to a significant degree (a) the safety
730 or physical or mental integrity of the participants of the trial; or b) the scientific value
731 of the trial. If a potential serious breach is identified by the Chief investigator,
732 Principal Investigator or delegates, the co-sponsors
733 (accord.seriousbreach@ed.ac.uk) will be notified within 24 hours. It will be the
734 responsibility of the co-sponsors to assess the impact of the breach on the scientific
735 value of the trial, to determine whether the incident constitutes a serious breach and,
736 if so, report it to the REC.

737 All violations will be assessed by the sponsor(s) to ascertain if they meet the criteria
738 for a serious breach. If the sponsor(s) deem the incident to be a violation that does
739 not constitute a serious breach from the protocol when identified, corrective and
740 preventative actions will be taken where appropriate and they will be recorded in file
741 notes, held within the TMF and ISF.

742 *Study record retention*

743 All study documentation will be kept for a minimum of 5 years from the protocol
744 defined end of study point. When the minimum retention period has elapsed, study
745 documentation will not be destroyed without permission from the sponsor.

746

747 *End of study*

748 The end of study date was finalised in the protocol after the study commenced; the
749 agreed end of study date is 31/12/2016. The Investigators and/or the trial steering
750 committee and/or the co-sponsor(s) have the right at any time to terminate the study
751 for clinical or administrative reasons.

752 The end of the study will be reported to the REC within 90 days, or 15 days if the
753 study is terminated prematurely. The Investigators will inform participants of the
754 premature study closure and ensure that the appropriate follow up is arranged for all
755 participants involved. A summary report of the study will be provided to the REC and
756 Regulatory Authority within 1 year of the end of the study.

757

758 **REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS**

759 Ownership of the data arising from this study resides with the study team. On
760 completion of the study, the study data will be analysed and tabulated, and a clinical
761 study report will be prepared in accordance with good clinical practice guidelines.
762 The clinical study report will be used as the basis for publication and presentation at
763 scientific meetings. Investigators have the right to publish orally or in writing the
764 results of the study. Summaries of results will also be made available to Investigators
765 for dissemination within their clinics (where appropriate and according to their
766 discretion).

767

768 **DISCUSSION**

769 The data provided by this study will inform the information given to women about
770 reduced fetal movements and their management when they present to maternity

services; which has been recurrently identified by Confidential Enquiries into antepartum stillbirths as suboptimal^{26 27}. Data from the AFFIRM study will be able to be compared to results from two other active studies which aim to improve mothers awareness and reporting of reduced fetal movements. My Babies Movement (ACTRN 12614000291684) is stepped-wedge cluster trial of a mobile phone application to help women get to know their baby's movements, to be mindful of movements every day and not to wait to report concerns to their maternity care provider. The Mindfetalness study (NCT02865759) is a cluster trial of 39,000 women randomised to routine antenatal care or the Mindfetalness brochure and website.⁴⁵ Women participating in the Mindfetalness process will spend 15 minutes each day getting to know their babies movements and will specifically be encouraged to contact their health provider if their perceive reduced fetal movements. This primary outcome of this study is an Apgar score <7 at 5 minutes; stillbirth and perinatal deaths will be recorded as tertiary endpoints of this study.⁴⁵ These large studies will provide much needed robust evidence to determine whether increased maternal awareness of reduced fetal movements combined with a standardised management protocol to identify acute or chronic fetal compromise can reduce stillbirth³².

PEER REVIEW

This project has been peer reviewed internally, and was externally peer reviewed during the process of securing funding from the Chief Scientist's Office of the Scottish Government, Tommy's and Sands.

FUNDING

The AFFIRM study is investigator initiated and funded by Chief Scientist Office, Scottish Government (CZH/4/882), Tommy's and Sands, the Stillbirth and Neonatal Death Charity. CJW was supported in this work by NHS Lothian via the Edinburgh

798 Clinical Trials Unit. AEPH is supported by a Clinician Scientist fellowship from the
799 National Institute for Health Research (NIHR; CS-2013-009). This protocol presents
800 independent research funded by the National Institute for Health Research (NIHR).
801 The views expressed are those of the author(s) and not necessarily those of the
802 NHS, the NIHR or the Department of Health.

803

804 **ACKNOWLEDGEMENTS**

805 The authors would like to acknowledge the support of Perinatal Ireland and Dr Mary
806 Higgins (University College Dublin, National Maternity Hospital, Dublin).

807

808 **CONTRIBUTIONS**

809 Contributors AEPH, CJW, SJES, CJC, SCB, MRD, SW and JEN were involved in
810 developing the trial design. AEPH, CJW, SJES, AR and JEN were involved in
811 drafting and revision of the article. CJW and AR were involved in drafting the
812 statistical aspects of the protocol. JS provided feedback on behalf of a stakeholder
813 organisation. AEPH, CJW, SJES, CJC, SCB, JFF, MG, AH, FMM, EM, AR, MRD, JS,
814 SW and JEN were involved in preparing the overall study design. AEPH, JEN and
815 MRD prepared education videos for online training. AEPH, SJES, SJS, MG, AH,
816 FMM and JEN facilitated recruitment of sites. AEPH, CJW, SJES, CJC, SCB, JFF,
817 MG, AH, FMM, EM, AR, MRD, JS, SW and JEN will be involved in the collection,
818 management, analysis and interpretation of data and final writing of the trial report.

819

820 **COMPETING INTERESTS**

821 None declared.

822

823

824

825

826

827

828

822 ABBREVIATIONS

823	ACCORD	Academic and Clinical Central Office for Research & Development -
824		Joint office for University of Edinburgh and NHS Lothian
825	BMI	Body Mass Index
826	CTG	Cardiotocograph
827	CTIMP	Clinical Trial of an Investigational Medicinal Product
828	ECTU	Edinburgh Clinical Trials Unit
829	FGR	Fetal growth restriction
830	MHRA	Medicines and Healthcare products Regulatory Agency
831	NICE	National Institute for Health and Social Care Excellence
832	NIHR	National Institute for Health Research
833	NIMATS	Northern Ireland Maternity Statistics database
834	NRPS	National Perinatal Reporting System
835	ONS	Office of National Statistics
836	PSANZ	Perinatal Society of Australia and New Zealand
837	RCOG	Royal College of Obstetricians and Gynaecologists
838	R&D	Research and Development
839	REC	Research Ethics Committee
840	RFM	Reduced Fetal Movements
841	SPIMMR	Scottish Perinatal and Infant Mortality and Morbidity Report
842	TMF	Trial Master File
843	TSC	Trial Steering Committee
844	WHO	World Health Organisation

845

846

847 REFERENCES

848 1. Curtis L, Burns A. Unit Costs of Health and Social Care 2015 Canterbury: Personal
849 Social Services Research Unit, The University of Kent, 2015.

850 2. Warland J, O'Brien LM, Heazell AE, Mitchell EA. An international internet survey of
851 the experiences of 1,714 mothers with a late stillbirth: the STARS cohort
852 study. *BMC pregnancy and childbirth* 2015;15:172.

853 3. Flenady V, Koopmans L, Middleton P, Froen JF, Smith GC, Gibbons K, et al.
854 Major risk factors for stillbirth in high-income countries: a systematic review
855 and meta-analysis. *Lancet* 2011;377(9774):1331-40.

856 4. Manktelow BM, Smith LK, Seaton SE, Hyman-Taylor P, Kurinczuk JJ, Field DJ, et
857 al. Perinatal Mortality Surveillance Report - UK Perinatal Deaths for births
858 from January to December 2014. Leicester:: The Infant Mortality and
859 Morbidity Group, Department of Health Sciences, University of Leicester.,
860 2016.

861 5. Sadovsky E, Polishuk WZ. Fetal movements in utero: nature, assessment,
862 prognostic value, timing of delivery. *Obstet Gynecol* 1977;50(1):49-55.

863 6. Flenady V, Middleton P, Smith GC, Duke W, Erwich JJ, Khong TY, et al. Stillbirths:
864 the way forward in high-income countries. *Lancet* 2011;377(9778):1703-17.

865 7. Heazell AE, Whitworth MK, Whitcombe J, Glover SW, Bevan C, Brewin J, et al.
866 Research priorities for stillbirth: process overview and results from UK
867 Stillbirth Priority Setting Partnership. *Ultrasound Obstet Gynecol*
868 2015;46(6):641-7.

869 8. Heazell AE, Froen JF. Methods of fetal movement counting and the detection of
870 fetal compromise. *J Obstet Gynaecol* 2008;28(2):147-54.

871 9. Stacey T, Thompson JM, Mitchell EA, Ekeroma AJ, Zuccollo JM, McCowan LM.
872 The Auckland Stillbirth study, a case-control study exploring modifiable risk
873 factors for third trimester stillbirth: methods and rationale. *The Australian &*
874 *New Zealand journal of obstetrics & gynaecology* 2011;51(1):3-8.

- 1
2
3 875 10. Ptacek I, Sebire NJ, Man JA, Brownbill P, Heazell AE. Systematic review of
4
5 876 placental pathology reported in association with stillbirth. *Placenta*
6
7 877 2014;35(8):552-62.
8
9 878 11. Warrander LK, Heazell AE. Identifying placental dysfunction in women with
10
11 879 reduced fetal movements can be used to predict patients at increased risk of
12
13 880 pregnancy complications. *Medical hypotheses* 2011;76(1):17-20.
14
15 881 12. Vintzileos AM, Fleming AD, Scorza WE, Wolf EJ, Balducci J, Campbell WA, et al.
16
17 882 Relationship between fetal biophysical activities and umbilical cord blood gas
18
19 883 values. *Am J Obstet Gynecol* 1991;165(3):707-13.
20
21 884 13. Warrander LK, Batra G, Bernatavicius G, Greenwood SL, Dutton P, Jones RL, et
22
23 885 al. Maternal perception of reduced fetal movements is associated with altered
24
25 886 placental structure and function. *PloS one* 2012;7(4):e34851.
26
27 887 14. Winje BA, Roald B, Kristensen NP, Froen JF. Placental pathology in pregnancies
28
29 888 with maternally perceived decreased fetal movement--a population-based
30
31 889 nested case-cohort study. *PloS one* 2012;7(6):e39259.
32
33 890 15. Holm Tveit JV, Saastad E, Stray-Pedersen B, Bordahl PE, Froen JF. Maternal
34
35 891 characteristics and pregnancy outcomes in women presenting with decreased
36
37 892 fetal movements in late pregnancy. *Acta Obstet Gynecol Scand*
38
39 893 2009;88(12):1345-51.
40
41 894 16. Healthcare Improvement Scotland. Scottish Perinatal and Infant Mortality and
42
43 895 Morbidity Report 2010. Edinburgh: Healthcare Improvement Scotland, 2012.
44
45 896 17. Gardosi J, Kady SM, McGeown P, Francis A, Tonks A. Classification of stillbirth
46
47 897 by relevant condition at death (ReCoDe): population based cohort study. *BMJ*
48
49 898 (*Clinical research ed* 2005;331(7525):1113-7.
50
51 899 18. Saastad E, Winje BA, Stray Pedersen B, Froen JF. Fetal movement counting
52
53 900 improved identification of fetal growth restriction and perinatal outcomes--a
54
55 901 multi-centre, randomized, controlled trial. *PloS one* 2011;6(12):e28482.
56
57
58
59
60

1
2
3 902 19. Mangesi L, Hofmeyr GJ, Smith V, Smyth RM. Fetal movement counting for
4
5 903 assessment of fetal wellbeing. *Cochrane Database Syst Rev*
6
7 904 2015(10):CD004909.
8
9 905 20. Grant A, Elbourne D, Valentin L, Alexander S. Routine formal fetal movement
10
11 906 counting and risk of antepartum late death in normally formed singletons.
12
13 907 *Lancet* 1989;2(8659):345-9.
14
15 908 21. National Institute for Health and Clinical Excellence. Clinical Guideline 62 -
16
17 909 Antenatal care: routine care for the health pregnant woman. London: National
18
19 910 Institute for Health and Clinical Excellence, 2008.
20
21 911 22. Sergent F, Lefevre A, Verspyck E, Marpeau L. Decreased fetal movements in the
22
23 912 third trimester: what to do? *Gynecol Obstet Fertil* 2005;33(11):861-9.
24
25 913 23. Froen JF, Heazell AE, Tveit JV, Saastad E, Fretts RC, Flenady V. Fetal
26
27 914 movement assessment. *Seminars in perinatology* 2008;32(4):243-6.
28
29 915 24. Saastad E, Vangen S, Froen JF. Suboptimal care in stillbirths - a retrospective
30
31 916 audit study. *Acta Obstet Gynecol Scand* 2007;86(4):444-50.
32
33 917 25. Froen JF, Arnestad M, Frey K, Vege A, Saugstad OD, Stray-Pedersen B. Risk
34
35 918 factors for sudden intrauterine unexplained death: epidemiologic
36
37 919 characteristics of singleton cases in Oslo, Norway, 1986-1995. *Am J Obstet*
38
39 920 *Gynecol* 2001;184(4):694-702.
40
41 921 26. Confidential Enquiry into Stillbirths and Deaths in Infancy. 8th Annual Report, 1
42
43 922 January–31 December 1999. London: Maternal and Child Health Research
44
45 923 Consortium, 2001.
46
47 924 27. Manktelow BM, Smith LK, Evans TA, Hyman-Taylor P, Kurinczuk JJ, Field DJ, et
48
49 925 al. Perinatal Mortality Surveillance Report - UK Perinatal Deaths for births
50
51 926 from January to December 2013. . Leicester:: The Infant Mortality and
52
53 927 Morbidity Group, Department of Health Sciences, University of Leicester.,
54
55 928 2015.
56
57
58
59
60

- 1
2
3 929 28. Linde A, Pettersson K, Radestad I. Women's Experiences of Fetal Movements
4
5 930 before the Confirmation of Fetal Death--Contractions Misinterpreted as Fetal
6
7 931 Movement. *Birth* 2015;42(2):189-94.
8
9 932 29. Preston S, Mahomed K, Chadha Y, Flenady V, Gardener G, MacPhail J, et al.
10
11 933 Clinical practice guideline for the management of women who report
12
13 934 decreased fetal movements. Brisbane,: Australia and New Zealand Stillbirth
14
15 935 Alliance, 2010.
16
17 936 30. Royal College Of Obstetricians and Gynaecologists. Management of Reduced
18
19 937 Fetal Movements. London: RCOG, 2011.
20
21 938 31. Tveit JV, Saastad E, Stray-Pedersen B, Bordahl PE, Flenady V, Fretts R, et al.
22
23 939 Reduction of late stillbirth with the introduction of fetal movement information
24
25 940 and guidelines - a clinical quality improvement. *BMC pregnancy and childbirth*
26
27 941 2009;9:32.
28
29 942 32. Hofmeyr GJ, Novikova N. Management of reported decreased fetal movements
30
31 943 for improving pregnancy outcomes. *Cochrane Database Syst Rev*
32
33 944 2012;4:CD009148.
34
35 945 33. Froen JF, Tveit JV, Saastad E, Bordahl PE, Stray-Pedersen B, Heazell AE, et al.
36
37 946 Management of decreased fetal movements. *Seminars in perinatology*
38
39 947 2008;32(4):307-11.
40
41 948 34. Dutton PJ, Warrander LK, Roberts SA, Bernatavicius G, Byrd LM, Gaze D, et al.
42
43 949 Predictors of poor perinatal outcome following maternal perception of reduced
44
45 950 fetal movements--a prospective cohort study. *PloS one* 2012;7(7):e39784.
46
47 951 35. Royal College Of Obstetricians and Gynaecologists. The Investigation And
48
49 952 Management Of The Small-For-Gestational-Age Fetus. London: RCOG,
50
51 953 2013.
52
53 954 36. Heazell AE, Green M, Wright C, Flenady V, Froen JF. Midwives' and
54
55 955 obstetricians' knowledge and management of women presenting with
56
57 956 decreased fetal movements. *Acta Obstet Gynecol Scand* 2008;87(3):331-9.
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

957 37. NHS England. Saving Babies' Lives - A care bundle for reducing stillbirth. Leeds:
958 Acute Care Policy Unit, 2015.

959 38. Tveit JV, Saastad E, Stray-Pedersen B, Bordahl PE, Flenady V, Fretts R, et al.
960 Correction: Reduction of late stillbirth with the introduction of fetal movement
961 information and guidelines - a clinical quality improvement. *BMC pregnancy*
962 *and childbirth* 2010;10:49.

963 39. Winje BA, Wojcieszek AM, Gonzalez-Angulo LY, Teoh Z, Norman J, Froen JF, et
964 al. Interventions to enhance maternal awareness of decreased fetal
965 movement: a systematic review. *Bjog* 2016;123(6):886-98.

966 40. Mitchell ML. Fetal brain to liver weight ratio as a measure of intrauterine growth
967 retardation: analysis of 182 stillborn autopsies. *Modern pathology : an official*
968 *journal of the United States and Canadian Academy of Pathology, Inc*
969 2001;14(1):14-9.

970 41. Barbaux S, Erwich JJ, Favaron PO, Gil S, Gallot D, Golos TG, et al. IFPA
971 meeting 2014 workshop report: Animal models to study pregnancy
972 pathologies; new approaches to study human placental exposure to
973 xenobiotics; biomarkers of pregnancy pathologies; placental genetics and
974 epigenetics; the placenta and stillbirth and fetal growth restriction. *Placenta*
975 2015;36 Suppl 1:S5-10.

976 42. Coleman SJ, Gerza L, Jones CJ, Sibley CP, Aplin JD, Heazell AE. Syncytial
977 nuclear aggregates in normal placenta show increased nuclear condensation,
978 but apoptosis and cytoskeletal redistribution are uncommon. *Placenta*
979 2013;34(5):449-55.

980 43. Hemming K, Girling A. A menu-driven facility for power and detectable-difference
981 calculations in stepped-wedge cluster-randomized trials. *The Stata Journal*
982 2014;14:363-80.

- 1
2
3 983 44. Jokhan S, Whitworth MK, Jones F, Saunders A, Heazell AE. Evaluation of the
4
5 984 quality of guidelines for the management of reduced fetal movements in UK
6
7 985 maternity units. *BMC pregnancy and childbirth* 2015;15:54.
8
9 986 45. Radestad I, Akselsson A, Georgsson S, Lindgren H, Pettersson K, Steineck G.
10
11 987 Rationale, study protocol and the cluster randomization process in a
12
13 988 controlled trial including 40,000 women investigating the effects of
14
15 989 mindfetalness. *Sexual & reproductive healthcare : official journal of the*
16
17 990 *Swedish Association of Midwives* 2016;10:56-61.
18
19 991
20
21 992
22
23
24 993
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

994 **FIGURE LEGENDS**

995 Figure 1 - Stepped wedge design. The shaded areas (both light and dark) indicate
996 periods in which the interventions are being implemented. The lighter areas indicate
997 the “transition” period during which data will not be collected for the control or
998 intervention group. The order in which hospital groupings implement the interventions
999 will be determined via randomization.

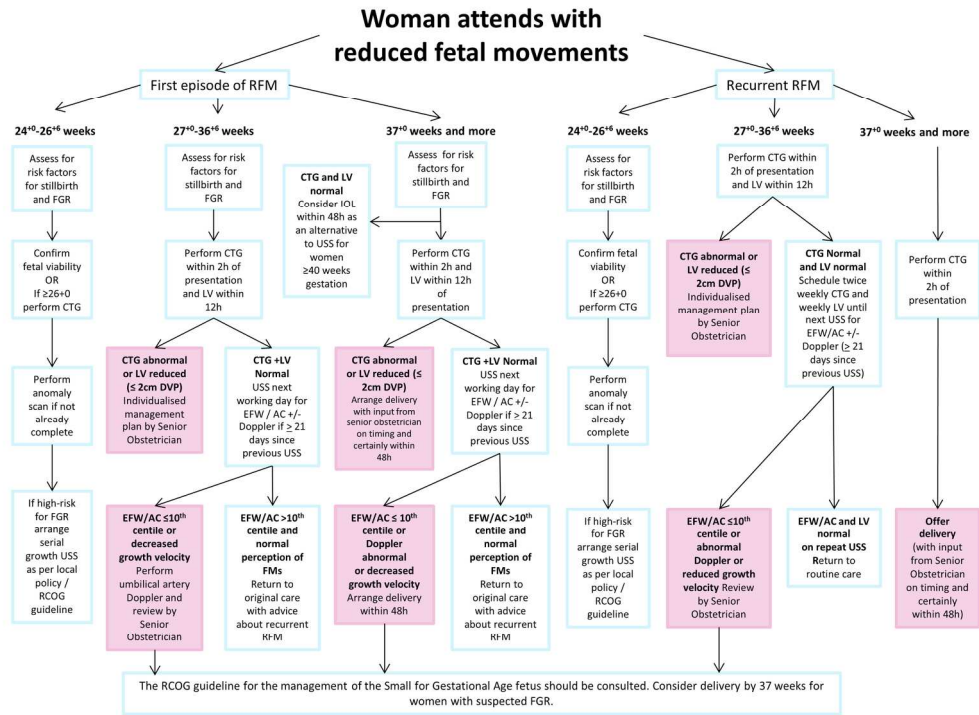
1000 Figure 2 – Flow chart for the management of women presenting with reduced fetal
1001 movements for sites implementing the AFFIRM study. Abbreviations: AC - abdominal
1002 circumference, CTG- cardiotocograph, DVP - deepest vertical pool, EFW - estimated
1003 fetal weight, FGR - fetal growth restriction, LV - liquor volume, RFM - reduced fetal
1004 movement, USS - ultrasound scan.

Hospital groupings	Months since Start of Trial								
	1-4	5-8	9-12	13-16	17-20	21-24	25-28	29-32	33-36
1-3									
4-6									
7-9									
10-12									
13-15									
16-18									
19-21									
22-24									

Stepped wedge design. The shaded areas (both light and dark) indicate periods in which the interventions are being implemented. The lighter areas indicate the "transition" period during which data will not be collected for the control or intervention group. The order in which hospital groupings implement the interventions will be determined via randomization.

190x142mm (300 x 300 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



Flow chart for the management of women presenting with reduced fetal movements for sites implementing the AFFIRM study. Abbreviations: AC - abdominal circumference, CTG- cardiotocograph, DVP - deepest vertical pool, EFW - estimated fetal weight, FGR - fetal growth restriction, LV - liquor volume, RFM - reduced fetal movement, USS - ultrasound scan.

190x142mm (300 x 300 DPI)

WHO TO CONTACT IF YOU ARE CONCERNED: (space for sticky with local contact information)



APS Group Scotland
DPPAS33137
Version 3 March 2015



In touch with YOUR BABY

A guide to your baby's
movements during
pregnancy



For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>

Why are my baby's movements important?

Why are we asking women to get to know their baby's movements?

One of the easiest ways to tell if your baby is healthy is to be aware of how much he or she is moving. Every baby is different and we are asking women to take time to become familiar with their baby's own individual pattern of movements. A reduction or change in **your** baby's movements is what is important.

What can affect my baby's movements?

You are less likely to be aware of your baby's movements when active or busy. Some drugs e.g. strong pain relief or sedatives can get into an unborn baby's circulation and affect the movements. Alcohol and smoking (active and passive smoking) may also affect the baby.

Why are my baby's movements important?

If you notice your baby is moving less than usual, or the pattern of movements has changed, this could be the first sign that your baby may not be well or is not growing properly in the womb. Research has shown that a reduction in the baby's movements may indicate an increased risk of stillbirth. You may hear your midwife or doctor referring to 'reduced fetal movement', or RFM for short.

What are the risks of stillbirth?

Stillbirth affects one in 200 babies after 24 weeks gestation and is one of the most common of the serious complications of pregnancy, affecting the lives of around 4,000 families every year in the UK.

One of the easiest ways to tell if your baby is healthy is to see how much he or she is moving. This booklet tells you what to look out for during your pregnancy.

Every baby is different. It is good to get to know your baby's own movements and the pattern of their sleeping and waking and report to us if you notice a reduction in these movements.



Try to get to know the times of the day when you are most likely to feel your baby move.



18-24 WEEKS



24-36 WEEKS



Most women begin to feel their baby move between 18-24 weeks. At first it may feel like 'bubbles', 'flutterings' or 'like trapped wind'. These are often very short and stop and start. It might take you a little while to be sure what you are feeling. But you will soon get to know the feelings. If this is your second baby, you will know what to look out for and may recognise your baby moving sooner.

Everyone is different when it comes to their movements. There are many reasons you might not feel movements as early as you expect. This includes your body weight, the position of your baby and the location of your placenta. What is important is your baby is growing well. Your midwife will be able to discuss this with you further at your 22 week check.

You will have your own way of describing your baby's own movements. Women often describe their baby's movements as 'rolling', 'kicking', 'pushing', 'jabs', 'elbowing' and 'stretches'.

Between 24-36 weeks you will start to recognise your baby's movements more quickly and become more used to the feeling. It is usually easier to feel your baby's movements when you are lying down, e.g. at night time. It is harder to feel your baby move when you are on your feet and moving around.

Try to get to know the times of the day you are most likely to feel your baby move. This will help you to know if he or she is moving less than normal or if movements have stopped.

Occasionally your baby will get hiccups. These do not count as movements. If you are unsure what you should expect when your baby hiccups, speak to your midwife.



Appendix 2 - Audit of compliance with AFFIRM protocol

Compliance with the AFFIRM management protocol (the management plan for women presenting with reduced fetal movement) will be determined by to means:

A) Telephone / email contact with Principal Investigators at each site to determine which aspects of the AFFIRM protocol have been implemented effectively. This will involve email contact with Principal Investigators to alert them to the request for information, an email detailing the information required, and then a phone call to elicit the information (unless it had already been supplied). Investigators will be asked which of the following elements they had implemented: issuing leaflets to all pregnant women, cardiotocography within 2 hours of presentation, measurement of amniotic fluid volume within 12 hours of presentation, growth scan by the next working day for all women presenting with reduced fetal movement (and who had not had a growth scan within the last three weeks, or who were not being induced within 48 hours), and induction of labour within 48 hours for women presenting with recurrent reduced fetal movement at or after 37 weeks gestation. "Effective implementation" was defined as the above management for 4/5 of these elements for 80% or more of the time.

B) An audit to determine whether the perception of the site Principal Investigator is supported by review of actual decision making will be performed for the following elements: cardiotocography within 2 hours of presentation, measurement of amniotic fluid volume within 12 hours of presentation, growth scan by the next working day for all women presenting with reduced fetal movement (and who had not had a growth scan within the last three weeks, or who were not being induced within 48 hours), and induction of labour within 48 hours for women presenting with recurrent reduced fetal movement at or after 37 weeks gestation.

This will be conducted by asking sites to complete an audit of the management of all women presenting with reduced fetal movement over the course of one calendar month. Sites will be asked to complete an audit form for each participant. The audit form template (see below) has been generated by the central

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

AFFIRM study team; anonymized forms will be analysed centrally. There will not be an attempt to corroborate Principal Investigator perception of the proportion of women who were given leaflets, nor will there be any attempt to incorporate the proportion of staff who had completed the e-learning package into analysis of whether any specific site has implemented the intervention or not.

For peer review only

Compliance with AFFIRM reduced fetal movements protocol, One month data collection AUDIT [Month & Year] Unit name: [Name of Hospital]

If you assess a woman with reduced fetal movements (RFM), please complete the questions below. Do not worry if the woman has been seen in other areas of the hospital by other staff, we would rather have multiple reports for the same woman than miss episodes of RFM.

INSERT Patient Sticker (or WRITE name and CHI /NHS number)				AREA WHERE SEEN (CIRCLE)								
				Triage / Labour ward / Day Assessment Unit (DAU)								
				Other (specify area i.e. antenatal ward): _____								
Date and time of presentation with reduced fetal movements.		DATE: ____/____/____ TIME ____:____ am / pm		GESTATION AND EDD:		____ WEEKS ____ DAYS EDD: _____						
Referred by (TICK BOX):		Self	Community Midwife	GP	ANC	Triage	DAU	Other (specify: _____)				
What was the primary reason for attending/phoning? (TICK BOX):		Reduced Fetal Movements			Other (specify: _____)							
How many times has the woman attended before this visit, with RFM? (TICK BOX):		None – first attendance		Once previously	Unknown	Multiple times (please provide the gestation at each presentation i.e. 30+6)		1	2	3	4	5
What was the time interval from the woman first being aware of reduced fetal movements and attending the hospital (in hours)?						HOURS: _____						
Has she been given a leaflet “Your baby’s movements in pregnancy”? (TICK BOX):		Yes – she already has one		Yes – I have given one to her today		Locally Created Leaflet Given		NO				
Has this woman had a growth USS in this pregnancy? (TICK BOX):		No, she has not had a growth scan		Yes, within the last 3 weeks (date of scan): DATE: ____/____/____		Yes, but more than 3 weeks ago (date of scan): DATE: ____/____/____						

CONTINUATION: NHS/ CHI NUMBER:

Are any of the following risk factors for Fetal growth restriction present (CIRCLE all that apply)?							
Age ≥40 or ≤16	Smoker ≥20cpd	Known or suspected growth restriction	Congenital anomaly	Raised BP (essential hypertension, pre-eclampsia or pregnancy induced hypertension)	Previous pre-eclampsia	Diabetes or gestational diabetes	Previous FGR or stillbirth
What investigations were conducted during this episode of reduced fetal movement?							
Please record below the date and time that these investigations were completed or indicate if not performed.					Please provide the results (CIRCLE):		
CTG	Not performed	<input type="checkbox"/>	DATE: __/__/____	TIME: ____:____ am/pm	Normal / Suspicious / Pathological		
			<u>Computerised CTG</u> : YES / NO (CIRCLE)				
Liquor volume assessment on scan	Not performed	<input type="checkbox"/>	DATE: __/__/____	TIME: ____:____ am/pm	Normal / Reduced / Increased		
Growth scan	Not performed	<input type="checkbox"/>	DATE: __/__/____	TIME: ____:____ am/pm	Normal / EFW < 10 th centile/ AC < 10 th centile / EFW and AC < 10 th centile		
Umbilical Artery Doppler	Not performed	<input type="checkbox"/>	DATE: __/__/____	TIME: ____:____ am/pm	Normal/.> 95 th centile/absent EDF/reversed EDF		
MCA Doppler	Not performed	<input type="checkbox"/>	DATE: __/__/____	TIME: ____:____ am/pm	Normal/<5 th centile		
DELIVERY METHOD (If available)							
Was the woman offered induction of labour	YES / NO (CIRCLE) IF Yes, please provide date, time and method of the induction:			DATE: ____/____/____ TIME: ____:____ am/pm			
Was the woman offered elective caesarean section as a result of the reduced fetal movement?	YES / NO (CIRCLE) IF Yes, please provide date, time and reason:			DATE: ____/____/____ TIME: ____:____ am/pm		Please provide the reason for the elective Caesarean section:	



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	____ Page 1 ____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	____ Page 4 ____
	2b	All items from the World Health Organization Trial Registration Data Set	_Included throughout protocol_
Protocol version	3	Date and version identifier	____ Page 4 ____
Funding	4	Sources and types of financial, material, and other support	____ Page 28 ____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	_Names and affiliations Page 1 and 2; Contributions Page 28_
	5b	Name and contact information for the trial sponsor	____ Page 24 ____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	_Not applicable_

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	___Page 24___
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	__Pages 5-11__
	6b	Explanation for choice of comparators	__Pages 8-9___
Objectives	7	Specific objectives or hypotheses	__Pages 11-12__
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	__Pages 13- 14 and Figure 1 ___
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	__Pages 13 & 16__
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	__Pages 14-15__
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	__Pages 17-18 and Figure 2__
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	__Not applicable in AFFIRM trial__
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	__Pages 17-18__
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	__Not applicable__

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	__Pages 12-13__
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	__Randomisation by site explained in Figure 1 and Pages 13-14__
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	__Pages 21-22__
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	__Page 22__
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	__Page 17__
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	__Page 17__
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	__Page 17__
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	__Page 17__
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	__Not applicable in AFFIRM study__

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	__Pages 18-21__
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	__Not applicable__
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	__Pages 19-20__
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	__Pages 22-23__
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	__Page 23__
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	__Pages 22-23__

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	_DMC not required, explanation Pg 24__
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	__Pages 18, 25-26__
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	__Page 24__
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	__Page 13__

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	__Page 25__
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	__Page 25__
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	__Page 25__
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	__Not applicable__
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	__Page 20__
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	__Page 29__
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	__Page 27__
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	__Page 24__
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	__Page 27__
	31b	Authorship eligibility guidelines and any intended use of professional writers	__Page 28__
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	__Not applicable__

Appendices

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_Not Applicable__
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_Not Applicable__

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](#)" license.

BMJ Open

Can Promoting Awareness of Fetal movements and Focussing Interventions Reduce Fetal Mortality? - A stepped wedge cluster randomised trial (AFFIRM)

Journal:	BMJ Open
Manuscript ID	bmjopen-2016-014813.R3
Article Type:	Protocol
Date Submitted by the Author:	02-Mar-2017
Complete List of Authors:	<p>Heazell, Alexander; University of Manchester, Maternal and Fetal Health Research Centre</p> <p>Weir, Christopher; University of Edinburgh, MRC Hub for Trials Methodology Research; Edinburgh Clinical Trials Unit</p> <p>Stock, Sarah; Queen's Medical Research Institute, EH16 4TJ, Tommy's Centre for Maternal and Fetal Health, MRC Centre for Reproductive Health,; School of Women's and Infants' Health, University of Western Australia, Crawley WA 6009. (FMM)</p> <p>Calderwood, Catherine; The Scottish Government St Andrew's House, EH1 3DG., Chief Medical Officer for Scotland,</p> <p>CunninghamBurley, Sarah; University of Edinburgh, Public Health Sciences</p> <p>Froen, Frederik; Nasjonalt folkehelseinstitutt, Division of Epidemiology</p> <p>Geary, Michael; Rotunda Hospital, Parnell Square</p> <p>Hunter, Alyson; Royal Maternity Hospital, Grosvenor Road, BT12 6BB</p> <p>McAuliffe, Fionnuala; University College Dublin,</p> <p>Murdoch, Edile; Royal Infirmary of Edinburgh, NHS Lothian, EH16 4SA., Department of Neonatology</p> <p>Rodriguez, Aryelly; University of Edinburgh, (ECTU) Edinburgh Clinical Trials Unit</p> <p>Ross-Davie, Mary; NHS Education for Scotland, 3rd Floor, Hanover Buildings, 66 Rose Street, EH2 2NN.</p> <p>Scott, Janet; Sands, Victoria Charity Centre, Suite GF2 Ground Floor, 11 Belgrave Road, SW1V 1RB.</p> <p>Whyte, Sonia; Queen's Medical Research Institute, EH16 4TJ, Tommy's Centre for Maternal and Fetal Health, MRC Centre for Reproductive Health,</p> <p>Norman, Jane; , Queen's Medical Research Institute, EH16 4TJ</p>
Primary Subject Heading:	Obstetrics and gynaecology
Secondary Subject Heading:	Research methods
Keywords:	Reduced Fetal Movements, Perinatal Mortality, Stillbirth, Neonatal Death, Fetal Growth Restriction

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

1 Study Protocol

2 Can Promoting Awareness of Fetal movements and Focussing Interventions Reduce
3 Fetal Mortality? - A stepped wedge cluster randomised trial (AFFIRM)

4 Alexander E P HEAZELL,^{1,2} alexander.heazell@manchester.ac.uk

5 Christopher J WEIR,^{3,4} christopher.weir@ed.ac.uk

6 Sarah J E STOCK,^{5,6} sarah.stock@ed.ac.uk

7 Catherine J CALDERWOOD,⁷ catherine.calderwood@scotland.gsi.gov.uk

8 Sarah CUNNINGHAM-BURLEY,⁴ sarah.c.burley@ed.ac.uk

9 J Frederik FROEN,⁸ frederik.froen@fhi.no

10 Michael GEARY,⁹ mppgeary@gmail.com

11 Alyson HUNTER,¹⁰ alyson.hunter@belfasttrust.hscni.net

12 Fionnuala M MCAULIFFE,¹¹ fionnuala.mcauliffe@ucd.ie

13 Edile MURDOCH,¹² edile.murdoch@nhslothian.scot.nhs.uk

14 Aryelly RODRIGUEZ,^{3,4} aryelly.rodriguez@ed.ac.uk

15 Mary ROSS-DAVIE,¹³ mary.ross-davie@nes.scot.nhs.uk

16 Janet SCOTT¹⁴ janet.scott@uk-sands.org

17 Sonia WHYTE⁵ sonia.whyte@ed.ac.uk

18 Jane E NORMAN.⁵ jane.norman@ed.ac.uk

19

20 1. Maternal and Fetal Health Research Centre, Institute of Human Development,
21 University of Manchester. 2. St. Mary's Hospital, Central Manchester University
22 Hospitals NHS Foundation Trust, Manchester Academic Health Science Centre,
23 Manchester, M13 9WL. 3. Edinburgh Clinical Trials Unit, Edinburgh, UK 4. Centre for

24 Population Health Sciences, Usher Institute of Population Health Sciences and
25 Informatics, University of Edinburgh, Teviot Place, Edinburgh EH8 9AG. 5. Tommy's
26 Centre for Maternal and Fetal Health, MRC Centre for Reproductive Health, Queen's
27 Medical Research Institute, Edinburgh, EH16 4TJ.6. School of Women's and Infants'
28 Health, University of Western Australia, Crawley WA 6009. (FMM) 7. Chief Medical
29 Officer for Scotland, The Scottish Government St Andrew's House Edinburgh EH1
30 3DG. 8. Department of International Public Health, Norwegian Institute of Public
31 Health, PB 4404 Nydalen, N-0403 Oslo, Norway, 9. Rotunda Hospital, Parnell
32 Square, Dublin 1, Ireland. 10. Centre for Fetal Medicine, Royal Maternity Hospital,
33 Grosvenor Road, Belfast, BT12 6BB 11. UCD Obstetrics & Gynaecology, School of
34 Medicine, University College Dublin, Ireland. National Maternity Hospital, Dublin,
35 Ireland. 12. Department of Neonatology, Royal Infirmary of Edinburgh, NHS Lothian,
36 Edinburgh, EH16 4SA. 13. NHS Education for Scotland, 3rd Floor, Hanover
37 Buildings, 66 Rose Street, Edinburgh EH2 2NN. 14. Sands, Victoria Charity Centre,
38 Suite GF2 Ground Floor, 11 Belgrave Road, London, SW1V 1RB.

39

Abstract

Background - In 2013, the stillbirth rate in the UK was 4.2 per 1,000 live births, ranking 24th out of 49 high-income countries, with an annual rate of reduction of only 1.4% per year. The majority of stillbirths occur in normally formed infants, with (retrospective) evidence of placental insufficiency the commonest clinical finding. Maternal perception of reduced fetal movements (RFM) is associated with placental insufficiency and increased risk of subsequent stillbirth.

This study will test the hypothesis that the introduction of a package of care to increase women's awareness of the need for prompt reporting of RFM and standardised management to identify fetal compromise with timely delivery in confirmed cases, will reduce the rate of stillbirth. Following the introduction of a similar intervention in Norway the odds of stillbirth fell by 30%, but the efficacy of this intervention (and possible adverse effects and implications for service delivery) have not been tested in a randomised trial.

Methods - We describe a stepped wedge cluster trial design, in which participating hospitals in the UK and Ireland will be randomized to the timing of introduction of the care package. Outcomes (including the primary outcome of stillbirth) will be derived from detailed routinely collected maternity data, allowing us to robustly test our hypothesis. The degree of implementation of the intervention will be assessed in each site. A nested qualitative study will examine the acceptability of the intervention to women and health care providers and identify process issues including barriers to implementation.

Ethics and Dissemination – Ethical approval was obtained from the Scotland A Research Ethics Committee (Ref 13/SS/0001) and from Research and Development offices in participating maternity units. The study started in February 2014 and delivery of the intervention completed in December 2016. Results of the study will be

submitted for publication in peer-reviewed journals and disseminated to local investigating sites to inform education and care of women presenting with RFM.

Trial Registration

www.clinicaltrials.gov NCT01777022

Version

Protocol Version 4.2, 3rd February 2017

Keywords

Reduced Fetal Movements; Perinatal Mortality; Stillbirth; Neonatal Death; Fetal Growth Restriction.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This trial directly addresses the need for studies of the information given to women regarding fetal movements and the subsequent management of reduced fetal movements identified by Confidential Enquiries into Antepartum Stillbirths, Systematic Reviews and the Stillbirth Priority Setting Partnership.
- A stepped-wedge cluster trial design in combination with routinely collected maternity data allows the trial to be adequately powered to detect a difference in stillbirth as a primary outcome.
- The pragmatic nature of the study represents the potential impact of the introduction of such standardised care into clinical practice.
- The nested qualitative study will provide information regarding the acceptability of the intervention and identify barriers and facilitators to its adoption.
- The lack of information on resource use before and throughout the study period limits the ability to understand the consequences of the intervention on maternity unit workload.

92

For peer review only

93 INTRODUCTION

94 *Stillbirth*

95 Stillbirth, defined in the UK as a baby with no signs of life after 24 weeks of completed
96 pregnancy ¹, remains the major cause of perinatal mortality in high-income
97 environments, with a recent series of papers in the Lancet on stillbirth issue calling for
98 renewed action in this area ². There is no single “cause” of stillbirth, and a significant
99 proportion of stillbirths remain unexplained, but fetal growth restriction, maternal
100 hypertension and low socioeconomic status are amongst the identifiable risk factors ³.
101 The concept that more can be done to reduce stillbirth in the UK and Ireland is
102 supported by data showing a marked variation in rates between resource rich
103 countries, when similar definitions of stillbirth are used ². Notably, the UK has a higher
104 rate than comparable resource rich countries such as Germany, Netherlands, New
105 Zealand and Norway with rates in the UK some 50% greater than those of the
106 Netherlands. Disappointingly, the annual rate of reduction in stillbirth from 2000 to
107 2014 in the UK was only 1.4% compared to 6.8% in the Netherlands and 2.8% in New
108 Zealand ². Rates of stillbirth in Scotland (3.7 per 1,000 births in 2014) and Ireland, at
109 (4.4 per 1,000 livebirths in 2013) are similar to rates in England and Wales at 4.2 per
110 1,000 livebirths (England and Wales, 2014) ⁴. The reduction of avoidable harm for
111 women and babies is viewed as a major priority for Government and its agencies
112 throughout the UK and Ireland. Consequently, several initiatives have been
113 developed by national governments in the UK and Ireland including the Scottish
114 Government Stillbirth Working Group, NHS England Saving Babies’ Lives Care
115 Bundle and the Welsh Assembly 1000 Lives Plus strategy. These strategies have
116 identified the need for better evidence to guide efforts to prevent stillbirths.

117 Using a robust priority setting strategy ⁵ the Lancet Stillbirth’s series steering
118 committee identified issues around detection and management of reduced fetal
119 movements (RFM) amongst the top ten key research questions on prevention and

management of stillbirth⁶. This was confirmed in the UK-based Stillbirth Priority Setting partnership involving over 1,700 parents and professionals which identified two relevant issues among the highest ranked research questions regarding stillbirth: i) which investigations identify a fetus at risk of stillbirth after a mother believes she has experienced reduced fetal movements? and ii) would more accessible evidence-based information on signs and symptoms of stillbirth risk, designed to empower women to raise concerns with healthcare professionals, reduce the incidence of stillbirth?⁷ Thus, RFM has been identified as a highly-relevant area of study by parents, professionals and researchers.

Reduced Fetal Movements, Stillbirth and Placental Insufficiency

There is a clear association between maternal perception of RFM and late stillbirth dating back over four decades⁸. In a recent series of 2,000 women, the adjusted OR (95% CI) of late stillbirth in women with RFM (compared with controls) was 2.37 (1.29-4.35)⁹. One international study of 1,714 women who experienced a stillbirth found that 30% had noted significant RFM prior to the diagnosis of stillbirth¹⁰. Although the mechanisms have not been fully delineated, it is likely that RFM and stillbirth are linked by a common pathology, that of placental dysfunction¹¹. There is good evidence linking placental dysfunction and RFM. Compared to controls with an active fetus women who have fewer fetal movements on ultrasound scan immediately prior to caesarean section are more likely to have umbilical cord gas measurements indicative of acidaemia, hypoxaemia, and hypercapnia¹². Women delivering within one week of an episode of RFM show differences in placental structure and function which are reminiscent of those seen in fetal growth restriction (FGR) and stillbirth^{13 14}. Additionally, the odds of fetal growth restriction (FGR, defined as being at less than the 10th centile for gestation adjusted birthweight) were greater in women with RFM compared with controls (adjusted OR 1.6, 95% CI 1.1–2.2¹⁵). Taken together these

147 data are strong evidence that placental dysfunction is associated with RFM, and a
148 causative pathway seems likely.

149 The evidence linking placental dysfunction and stillbirth is even stronger; a systematic
150 review of placental pathology in stillbirths described abnormalities in up to 65% of
151 cases ¹⁰. Amongst the 291 stillbirths in Scotland in 2010, 137 (47%) had evidence of
152 placental dysfunction ¹⁶. Given that the placenta was examined in only 80% of
153 stillbirths, the true prevalence of placental dysfunction is likely to be higher. In
154 addition, between 20%-40% of stillborn babies are reported to have FGR, as defined
155 by a birthweight less than the 10th centile ¹⁷. Additionally, the Lancet report notes that
156 “placental pathologies accounted for one in four deaths across all gestational ages,
157 and were contributory or causal in more than half of cases” ⁶. Given that stillbirth is
158 strongly related to placental dysfunction, and RFM is a “biomarker” of placental
159 dysfunction then better management of women presenting with RFM focussing on the
160 detection of placental dysfunction might reduce the risk of stillbirth.

162 *Formal Fetal Movement Counting*

163 Although prenatal detection of FGR is improved by fetal movement counting ¹⁸, a
164 systematic review ¹⁹, and a large and influential cluster randomised trial (which
165 dominates the systematic review) showed that routine fetal movement counting using
166 the count to ten charts had no effect on perinatal mortality ²⁰. Thus, the National
167 Institute for Health and Social Care Excellence (NICE) recommended that “Routine
168 formal fetal movement counting should not be offered” ²¹. Importantly, the large
169 cluster randomised trial tested a specific alarm limit for RFM, but did not recommend
170 a specific management strategy for women who did present with RFM. There were
171 two important observations from this study, firstly that in both groups the perinatal
172 mortality rate was lower than contemporary or subsequent periods in the UK and
173 secondly that more women in the fetal movement counting arm came in with a live
174 baby who subsequently died compared with the control arm (19 vs 11), suggesting

1
2
3 175 that one reason the strategy failed to reduce perinatal mortality was inadequate
4
5 176 investigation and management of those presenting with RFM ²⁰.

6
7 177

8
9 178 *Optimal strategy for determining RFM to prompt maternal presentation to the*
10
11 179 *maternity service*

12
13 180 Maternal concern about RFM is a common reason to contact maternity services with
14
15 181 between 6-15% of women presenting during the third trimester.^{22 23} Nevertheless,
16
17 182 delays in reporting RFM to maternity care providers may increase the risk of adverse
18
19 183 outcome.^{24 25} The lack of good-quality information given to women about fetal
20
21 184 movements has been highlighted as an example of suboptimal care in Confidential
22
23 185 Enquiries into Antepartum Stillbirth.^{26 27} Qualitative studies suggest that women
24
25 186 frequently perceive RFM two days prior to the diagnosis of fetal death, and in some
26
27 187 cases contractions were misinterpreted as fetal movements.²⁸ Therefore, giving
28
29 188 information to women regarding fetal movements and when they should be
30
31 189 concerned about RFM is a key component of an intervention to reduce stillbirth.

32
33 190 However, giving clear information about RFM can be challenging as there is no
34
35 191 uniform threshold of fetal movements below which perinatal morbidity increases ²³,
36
37 192 and no evidence that a specific threshold performs better than maternal perception of
38
39 193 reduced fetal movements alone ⁸. Current guidelines from the RCOG and PSANZ ²⁹
40
41 194 ³⁰, informed by a large Norwegian study ³¹ suggest that it is maternal *perception* of
42
43 195 decreased fetal movement which is important. Therefore, information for pregnant
44
45 196 women in this study (shown in Supplementary File 1) described the importance of
46
47 197 fetal movements, the need to get to know normal fetal activity, how fetal movements
48
49 198 change in late pregnancy and who to contact if the mother perceives RFM. The
50
51 199 educational package aimed to ensure that these messages were reinforced by staff
52
53 200 behaviour at antenatal contacts.

54
55
56 201

57
58 202 *Optimal strategy for investigation and management of women presenting with RFM.*
59
60

203 A recent systematic review found there are no proven strategies for the investigation
204 and management of women presenting with RFM ³². Cardiotocography (CTG) is
205 routinely used to ascertain fetal wellbeing, and it is the cornerstone of the RCOG
206 guideline ³⁰. However, data from Norway, suggests that ultrasound assessment of
207 fetal size is often the most helpful investigation, performing well on both an absolute
208 basis, and compared with other interventions ³³. In a series of over 3,000 women with
209 RFM, ultrasound (including measurement of fetal biometry and liquor volume) was
210 found to be useful in detecting abnormalities in 11.6% of scans. In 71% of women in
211 whom an abnormality was found, ultrasound was the only technique that detected an
212 abnormality. Additionally, 85% of abnormalities detected by ultrasound, were
213 important in informing the clinical management of the woman ³³. These data are
214 supported by a smaller UK study which found that abnormalities detected on CTG or
215 ultrasound scan were most strongly associated with adverse outcome in women with
216 RFM, with identification of abnormal estimated fetal growth centile on scan being the
217 test most highly predictive of poor outcome ³⁴. Perhaps this is not surprising, given the
218 strong association between RFM and placental dysfunction and the central
219 importance of ultrasound in the identification and management of small for gestational
220 age babies ³⁵. Given these data, it is concerning that a survey of clinicians in Scotland
221 showed that fewer than 5% would routinely refer women with RFM for ultrasound
222 examination (unpublished data from June 2012), and a survey of 223 UK midwives
223 and obstetricians described that 17.9% of respondents would perform an ultrasound
224 scan ³⁶. These views of clinicians may reflect the variable quality of local guidelines,
225 which are frequently not based on national recommendations, even those for which
226 there is strong evidence ³⁷. The variation in information given to women and
227 subsequent management of RFM has been highlighted as sources of suboptimal care
228 in two confidential enquiries into antepartum stillbirth ^{26 27}. Therefore, we believe that
229 current investigation of women presenting with RFM is inadequate, hence using the
230 best available evidence, we have drafted what we consider to be a robust evaluation

231 protocol for investigation of women with RFM.

232

233 *Potentially efficacy of a package of intervention for RFM*

234 Supportive data for the package of interventions used in this study (information for
235 women and standardised management protocol) comes from a large observational
236 “clinical quality improvement study” in Norway which found a significant fall in rates of
237 stillbirth (from 3.0/1,000 to 2.0/1,000 [OR 0.67 95% CI 0.48–0.93]) after the
238 introduction of an intervention package consisting of written information for women
239 about awareness of RFM combined with consensus guidelines for health
240 professionals about their management ³¹. Although this study was not randomised,
241 and therefore constitutes only level II-3 evidence, it has informed recommendations
242 from the Royal College of Obstetricians and Gynaecologists (RCOG) and Perinatal
243 Society of Australia and New Zealand (PSANZ) that “women should be advised to be
244 aware of their baby’s individual pattern of movements and that if they are concerned
245 about a reduction in or cessation of fetal movementsthey should contact their
246 maternity unit” ^{29 30}. Following initial publication of the Norwegian study, a re-analysis
247 was required as discrepancies between stillbirth rates in the study and the Medical
248 Birth Registry of Norway were identified. This reanalysis found the reduction in
249 stillbirth rates was of borderline statistical significance (OR 0.72, 95% CI 0.50-1.03).
250 The authors concluded that further studies were needed to determine whether this
251 approach was associated with a reduction in stillbirth ³⁸.
252 Importantly, in the Norwegian study, there was no increase in the proportion of
253 women who presented with RFM when rates were compared before and after the
254 intervention ³¹. However, women with RFM presented significantly earlier to hospital
255 than they had hitherto, potentially allowing time for intervention to reduce perinatal
256 mortality. These data suggest that a package of interventions encouraging women
257 with RFM to present early to hospital, combined with a structured approach to their
258 management might reduce rates of stillbirth without contributing to a large increase in

admissions antenatally.

Potential harms of a package of care around increased awareness and optimised management of RFM

Any clinical intervention which aims to improve outcomes also has the ability to do harm. Thus, it is essential that the intervention proposed is rigorously evaluated using the gold standard technique of a randomised trial, rather than being introduced as a service development. When the study began, there was a small window of opportunity to do this, as the enthusiasm to improve current management of RFM is such that routine introduction of the package of care is unlikely to be delayed much further than the current scheduled end date of this study. Possible harms of a package of care consisting of a management plan for identification and delivery of the “at risk” fetus, together with strategies for increasing pregnant women’s awareness of the need to report early include increased maternal anxiety and increased intervention (including hospital admission, induction of labour and Caesarean section) which itself is associated with pregnancy related complications. The available evidence is reassuring on some of these issues. A systematic review of 23 publications from 16 studies found three studies involving 2,030 women addressing maternal concern and an additional three studies involving 1,468 women investigating maternal-fetal attachment. These demonstrated no evidence of increased maternal anxiety and results regarding maternal-fetal attachment were discordant.³⁹ In the Norwegian service development study, the package of care increased rates of follow up of women, but there was no increase in admissions overall, admissions for induction or admissions for emergency caesarean section ³¹ – again, whilst reassuring these outcomes require formal evaluation in a randomised and relevant setting to the UK and Republic of Ireland. The final possible harm of the package is around increased resource use, and the opportunity cost of focussing on RFM rather

286 than other potential methods to prevent stillbirth.

287

288 RATIONALE

289 The aim of this study is to test the hypothesis that a package of interventions
290 consisting of strategies for increasing pregnant women's awareness of the need to
291 report early when they perceive a reduction in fetal movements, followed with a
292 management plan for identification and delivery of the "at risk" fetus in such women,
293 will reduce rates of stillbirth.

294

295 STUDY OBJECTIVES

296 *Primary Objective*

297 The primary objective is to answer the research question 'Does the introduction of a
298 protocol for detection and management of decreased fetal movements reduce rates
299 of stillbirth?' The secondary objectives are to answer the following research
300 questions:

- 301 • What is the effect of the intervention on rates of caesarean section and induction
302 of labour?
- 303 • What is the effect of the intervention on rates of admission to the neonatal
304 intensive care unit?
- 305 • What is the effect of the intervention on the proportion of women with FGR
306 remaining undelivered by 40 weeks gestation?
- 307 • What is the acceptability of such a package of care to pregnant women and their
308 health care providers?
- 309 • What other process outcomes are influenced by the intervention, such as health
310 care provider/patient interactions?

311

312 **ENDPOINTS**

313 *Primary Outcome*

314 The primary endpoint is stillbirth (antepartum and intrapartum). We will use the UK
315 definition of stillbirth which is “a baby delivered without signs of life after 23⁺⁶ weeks”
316 ⁴. Where gestation is uncertain we will include all babies with a birth weight of 500g
317 or more.

318 *Secondary Endpoints*

319 Other measures of perinatal mortality including:

- 320 • Stillbirth at 37 weeks gestation and above
- 321 • Stillbirth at 28 weeks gestation and above (WHO definition of stillbirth)
- 322 • Stillbirth at 22 weeks gestation and above (international stillbirth alliance
323 definition)
- 324 • Stillbirths amongst normally formed infants of 22 weeks gestation and above,
325 24 weeks gestation and above, 28 weeks gestation and above and 37 weeks
326 gestation and above.
- 327 • Perinatal mortality (defined as stillbirth at 24 weeks gestation and above and
328 deaths in the first seven days of life)
- 329 • Rates of caesarean section
- 330 • Rates of induction of labour (for any indication)
- 331 • Rates of elective delivery (induction of labour and caesarean section prior to
332 the onset of labour) overall
- 333 • Rates of induction of labour at 39 weeks gestation or later
- 334 • Mean gestation at induction of labour

- 335 • Rates of admission to the neonatal unit (and their reasons)
- 336 • Rates of admission to the neonatal unit for more than 48 hours
- 337 • Rates of admission to the neonatal unit for term babies (those born at 37
- 338 weeks 0 days or greater)
- 339 • Proportion of infants with fetal growth restriction (less than the 5th centile,
- 340 customised for gender) remaining undelivered at or after 40 weeks gestation
- 341 • Birthweight centile (according to the Intergrowth birthweight centile calculator
- 342 at <https://intergrowth21.tghn.org>)
- 343 • Rates of spontaneous vaginal delivery
- 344 Other secondary outcomes are the baby parameters:
 - 345 • Gestation at birth
 - 346 • Proportion of babies born preterm (<37 weeks gestation)
 - 347 • Gender of the baby
 - 348 • Birthweight of the baby
 - 349 • Apgar score at 5 minutes
 - 350 • Proportion of babies with 5 minute Apgar score < 7
 - 351 • Proportion of babies with 5 minute Apgar score < 4
 - 352 • Resuscitation required at birth

353 We will also collect the following data: maternal age, maternity unit of delivery,
354 birthweight, gestation of delivery, parity, gestation, sex, smoking (current and ever),
355 maternal body mass index (BMI), number of babies (one or more), ethnicity (to allow
356 a customised birthweight centile to be generated), method of delivery, deprivation
357 category (where available) and other neonatal variables including Apgar score and
358 encephalopathy. Adjustment will be made for the following variables: (maternal age,

maternity unit of delivery, parity, smoking status, maternal BMI, number of babies
[one or more] and ethnicity)

361

STUDY DESIGN

This is a multicentre, stepped wedge cluster randomised trial of a package of care consisting of a management plan for identification and delivery of the ‘at risk’ fetus, together with strategies for increasing pregnant women’s awareness of the need to report RFM early. The trial developed from a planned quality improvement project proposed by the Scottish Government to reduce stillbirths. This was planned to emphasise the importance of fetal movement monitoring and was to be rolled out to all NHS maternity units in Scotland. However, prior to this change it was agreed that the roll out could be performed in such a way as to allow the assessment of the effect of the intervention, the stepped-wedge design would be the natural choice in this circumstance.

The study will take place in participating hospitals in the UK and Ireland (a complete list is available <http://www.crh.ed.ac.uk/affirm/randomised-hospitals/>). A nested qualitative study will examine the acceptability of the intervention to patients and health care providers and identify process issues (barriers to implementation). Clinical audit (detailed in Appendix 3) conducted after the change in practice will be used to determine the effect of interventions on process outcomes (e.g. number of women presenting with reduced fetal movements, interval between perceiving reduced fetal movements and presentation to hospital, number of ultrasound scans, number of admissions for induction of labour). A diagram indicating randomisation of hospital groupings in the stepped wedge design is shown in Figure 1.

The interventions will be introduced over a 32 month period. Data will be collected over a 36 month period. Data in the ‘active phase’ after introduction of the

intervention will be compared to data in the 'control phase' – the period during which usual care processes in study sites are followed from study start to the time of introduction of the intervention. Given that it will take individual units some time (a) to effect change in management in their unit from time of introduction of the intervention and (b) that it will take some time for this change in practice to impact on clinical outcomes, we plan a "washout" period of two months after the introduction of the intervention during which data will not be included in either group for analysis (Figure 1). Data will be collected four months after the last birth, a further two months has been included for data analysis, giving a total study duration of 42 months.

STUDY POPULATION

Number of participants

Participants will be those delivering at all the sites over the study period (36 months). All eligible women will be recruited to the cluster randomised controlled trial. Based on previous delivery numbers, after accounting for a washout period of two months (and assuming no withdrawals or losses to follow up) this is estimated to be a total of around 143,140 women per annum. A subset of around 30 participating women and 30 midwives, sonographers and obstetricians will be recruited to the nested qualitative study, which is based in the Scottish sites.

Inclusion criteria

We will include all women delivering at one of the participating maternity units for the duration of the study. Women who have been seen at any of the maternity units but who deliver at home will not be included. The duration of the study will be 42 months from the start of the trial (01/02/2014). For practical reasons, participants for the nested qualitative study will be recruited from the participating units in Scotland.

Exclusion criteria

- 411 We will exclude women as follows:
- 412 • Women for whom data on delivery outcomes is still unavailable four months after
 - 413 the date of delivery
 - 414 • Women delivering in the “washout” period in each unit.

415 Members of the trial management group and participants who do not
416 speak/understand English will be excluded from participating in the nested qualitative
417 study.

418 *Identifying participants*

419 Women will be identified from those whose data is included in routine data returns
420 from each unit. Potential participants for the nested qualitative study will be identified
421 from those attending antenatal clinics in participating hospitals, and/or local staff.

422 *Consenting participants*

423 The main study is a stepped wedge cluster randomised trial of a package of care
424 which would be introduced in many of the participating units regardless of whether
425 the trial was on-going or not and the trial uses only routinely collected data on
426 participants. The ethics committee indicated that formal individual patient consent is
427 not necessary for the main trial. Participants in the nested qualitative study will be
428 asked for individual consent.

429 *Screening for eligibility*

430 As participants are not directly recruited we will not perform any specific screening
431 tests for this aspect of this project. Participants for the nested qualitative study will
432 be: (i) Pregnant women attending hospitals who are participating in the main trial in
433 Scotland. Purposive sampling will ensure that the final sample set includes women
434 who have and who have not experienced RFM, both before and after the introduction
435 of the intervention; (ii) Hospital staff (including midwives, ultrasonographers and

obstetricians/radiologists) working in participating hospitals in Scotland. There will be no specific screening tests for eligibility for the nested qualitative study, except that women who have experienced a stillbirth in the index pregnancy will not be approached.

Ineligible and non-recruited participants

Potential participants for the nested qualitative study who are not approached or who decline will have no specific interventions / procedures.

Withdrawal of Study Participants

The nature of a cluster randomised study is such that it is not possible for the participant to withdraw from the “cluster” unless she changes maternity unit part way through her pregnancy. We plan to collect routinely recorded anonymised data; patients have the right to opt out of having their data used – if this happens their data would be excluded from the study database (e.g. under the Confidentiality and Security advisory Group Report 2002 and the Data Protection Act (1998) requirements for fair processing of data). Participants in the nested qualitative study who wish to withdraw will be allowed to do so. Their data will be retained and used, unless they additionally indicate that they wish to withdraw their data.

RANDOMISATION

Randomisation Procedures

This is a cluster-randomised, stepped-wedge design trial wherein maternity units rather than individual patients are randomised. All units will implement the fetal movement monitoring intervention at some point during the trial; the random element is the time point at which this will occur, the so-called “step” of the stepped-wedge design. Participating maternity units will be blinded to their randomly allocated time point until the time this is required to be revealed to enable the necessary training in the implementation of the intervention to be delivered. Primary and secondary

462 outcomes of the trial will be gathered in a blinded manner via routinely collected data
463 sources.

464 Maternity units which are in close proximity to each other will be grouped for the
465 purposes of randomisation. This will assist with the feasibility of delivering the training
466 for and implementation of the intervention. Furthermore, this local synchronisation of
467 the intervention implementation will minimise the chances of contamination
468 (introduction of the intervention prematurely) from maternity units which have already
469 implemented the intervention to those not yet randomised.

470 The order in which the groups of maternity units step in to implement the intervention
471 will be determined by computer generated random numbers from a uniform
472 distribution. The randomisation list will be held by the Edinburgh Clinical Trials Unit
473 (ECTU). The identities of the research team staff whose roles in the trial require them
474 to be unblinded to randomisation codes will be recorded in the trial master file (TMF).

475 *Treatment Allocation*

476 Participating sites will be randomised to different schedules for implementing the
477 intervention. All units will be providing conventional treatment at baseline according
478 to local practice – this is the treatment established before the study starts. Sites will
479 be randomised to “active” treatment in turn as described above. Active treatment will
480 consist of a package of care consisting of a management plan for identification and
481 delivery of the ‘at risk’ fetus, together with strategies for increasing pregnant women’s
482 awareness of the need to report RFM early. The recommended management plan for
483 identification and delivery of the “at risk” fetus is shown in Figure 2. Practice change
484 in the active units will be achieved by: (i) written/email information to all clinicians
485 (doctors, midwives and ultrasonographers) in each unit about the study protocol and
486 amendment of the local protocol for Reduced Fetal Movements (RFM) to that of the
487 study protocol; (ii) a short web-based training package taking approximately one hour
488 to complete for all clinicians in each centre and (iii) training /information sessions to

run in each unit and (iv) posters in each unit to describe the practice change. Strategies for encouraging clinicians to increase pregnant women's awareness of fetal movement will include all the above and also a fetal movement leaflet for pregnant women (shown in Supplementary Information 1). The Norwegian quality improvement study showed inconclusive results regarding the effect of the intervention in non-European women.⁴⁰ To attempt to address this, the AFFIRM information leaflet was available in 12 languages including: Arabic, Bengali, English, Hindi, Hungarian, Latvian, Lithuanian, Mandarin, Polish, Russian and Urdu. Furthermore, by including staff education which highlighted the need to ask women about fetal movements in routine antenatal consultations as many women as possible should have received information about what to do if they perceive RFM.

Once units have begun active treatment it is not anticipated that they will return to conventional treatment. We will conduct an audit of women presenting with reduced fetal movements and assess the proportion of staff completing the online training to assess the extent to which sites have followed the intervention plan. Units will be informed about treatment allocation as near as possible to the implementation of the "active" treatment. For practical purposes, we anticipate that each unit will need around three months' notice before the "active" treatment is introduced, hence units will be informed of the timing of their treatment allocation (step) three months before the active treatment is due to start. The treatment allocation will not be administered blind and there are no restrictions on concomitant care or other interventions during the study, hence there is no need for emergency unblinding and there are no stopping rules for the study.

512

513 DATA COLLECTION

514 For the main trial, data will be accessed from the information routinely collected
515 during the clinical management of the patient. For consistency, we will normally only

include data items which become available within four months after the delivery date in question, although we may seek advice from the independently-chaired trial steering committee (TSC) about exceptions as they arise. Different data sources will be used for different regions of the study: (i) In Scotland the source data will be SMR2 and the Scottish Birth record, (ii) In Ireland the source data will be the National Perinatal Reporting System (NRPS http://www.esri.ie/health_information/nprs), (iii) In Northern Ireland, the source data will be the Northern Ireland maternity Statistics database (NIMATS), (iv) In England and Wales, the source data will be the ONS, or other relevant body. Data will be collected retrospectively on an annual basis from all sources. We will assume that data unavailable four months after the woman delivered is likely to be unobtainable (but see note in Study Design section above). Thus, data on the first year of the study will be collected at month 16; data on the second year will be collected at month 28 etc.

Data are routinely collected. A formal request for data access will be made at the start of the study. This will require (i) in Scotland – Privacy Advisory Committee approval and a formal approach to NHS Scotland Information Services Division (ISD) (ii) in Ireland a formal approach to NRPS (iii) NIMATS in Northern Ireland (iv) in England and Wales a formal approach will be made to the relevant bodies.

Data will then be sent to the electronic Data Research and Innovation Service (eDRIS) National Safe Haven (NHS National Services Scotland) by secure file transfer protocol (or other similar) for storage and subsequent analysis within a secure project area (dedicated to the AFFIRM study). Further information on the National Safe Haven is available at <http://www.isdscotland.org/Products-and-Services/eDRIS/Becoming-an-eDRIS-User/#NSS-National-Safe-Haven>. Briefly, the National Safe Haven is located on a secure server, in which trusted and authorised researchers can analyse individual level data while maintaining the utmost

542 confidentiality. It is anticipated that all study analysis will be done within the Safe
543 Haven, using one of the available statistical packages (e.g. R, SPSS).

544 Identifiers on Scottish data within the National Safe Haven are concealed from
545 researchers. Data from outwith Scotland will be anonymised before submission to the
546 National Safe Haven. We propose that data submitted to the National Safe Haven
547 will be “anonymised” by the data provider. However, we propose that the
548 anonymisation link will be retained at the source so that it will be possible to re-link
549 data retrospectively. The rationale for retaining the ability of local data guardians to
550 re-link data is because it is important to retain the possibility of identifying individual
551 patients retrospectively. Examples include: (i) It is possible that some additional
552 important data may be available at a late stage on individual participants – e.g. in the
553 scenario where the woman or baby had a major adverse event and spent a long time
554 in hospital before discharge or death and (ii) Although our protocol and outcome
555 analysis does not require identifiable data, we believe this will be a ‘once in a lifetime’
556 study, and that subsequent secondary analyses could yield important information for
557 patients and for policy makers. If retrospective identification is not possible, this will
558 limit further analysis. One likely example of future analyses is to determine the effect
559 of the intervention on different causes of stillbirth. This is outwith the scope of the
560 current protocol, but could be done relatively straightforwardly, by linking nationally
561 recorded information on “cause” of stillbirth to our study database. We anticipate that
562 such additional analyses would require additional ethics approval, but without a
563 process by which to re-link data, it will not be possible to perform such subsequent
564 analyses.

565 All Investigators and study site staff involved with this study will comply with the
566 requirements of the Data Protection Act 1998 (or equivalent for those outwith the UK)
567 with regard to the collection, storage, processing and disclosure of personal

information and will uphold the Act's core principles. Published results will not contain any personal data that could allow identification of an individual participant.

In addition to the data recorded above, all sites will be asked to provide a copy of their guidelines around (i) maternal awareness of RFM and (ii) management of women presenting with RFM. Copies of guidelines will be sought by the study office (a) at the start of the study (b) immediately before initiation of the intervention in each specific unit and (c) six months after initiation of the intervention in each specific unit.

For the nested qualitative study, we will perform interviews of healthcare workers and a small nested cohort of pregnant women about their experiences of fetal movement and of this intervention. We shall ensure a diversity of age and include nulliparous and multiparous women (n=30 in total). Ten interviews will be conducted with each of the following groups of health care providers: obstetricians, midwives and sonographers/radiologists. The interviews will take a semi-structured format (sensitising and piloting interviews will be conducted prior to the commencement of the trial and in the first month of the nested qualitative study). This format will ensure the same categories of data will be obtained from each participant but also allow individual responses to be fully explored.

STATISTICS AND DATA ANALYSIS

Sample size calculation

The sample size is the number of women delivering in hospitals participating in the study. This was initially planned to include sites in Scotland, totalling around 58,000 deliveries per year with 16 consultant led maternity units, 20 smaller units each delivering less than 350 babies per year, and seven units delivering less than five births per year. The units involved in Perinatal Ireland (an all-Ireland research consortium across 7 academic sites in Ireland currently funded by the Health

Research Board, Ireland) have 50,000 births per year with seven large sites. Combining one or two of the smaller units and one larger unit into a single “hospital group” for each local area could provide 24 hospital “groups” – the details of hospital groupings will be reviewed and finalised immediately prior to randomisation. In total, 36 sites expressed interest in participating in the study, although 2 were unable to participate in the study and withdrew before randomisation. In total, 34 units were randomised, these were situated throughout the UK and Ireland (10 in England, 4 in Ireland, 15 in Scotland and 5 in Wales) with 143,140 births per annum.

We calculated statistical power using the methodology for stepped wedge designs proposed in Hussey and Hughes (2007).⁴¹ First, we analysed stillbirth event data from the Scottish Perinatal and Infant Mortality and Morbidity Report (SPIMMR) covering years 2005-2010¹⁶ to determine estimates of between- and within-unit variability in stillbirth rate. Analysis was by generalized linear mixed model for binary outcomes. The power calculation, as per equations (#7) and (#8) in⁴¹ assumed: significance level 5%; analysis by generalized linear mixed model; deliveries equally distributed across hospital groupings; baseline stillbirth rate 0.438%¹⁶; cluster coefficient of variation 0.333.

Finally, the statistical power depends on the number of groups in which the intervention is implemented at each stage of the stepped wedge design and the duration of recruitment at each “step”. Our study design proposes sequential introduction of the intervention into three hospital groups at a time in eight steps at four month intervals. This would give 92.4% power to detect a 30% risk reduction under the intervention and 80.7% power to detect a 25% reduction. A 30% risk reduction was seen in the Norwegian study; the anticipated effect sizes of 25% and 30% relative reduction take into account that the intervention will not have the power to reduce all stillbirths, since 20% of stillbirths in Ireland⁴² and 15% in Scotland¹⁶ are associated with congenital anomaly.

1
2
3 621 The power actually achieved in the study will be slightly lower, as deliveries during
4
5 622 the two month “transition” period following implementation of the intervention in a site
6
7 623 will not be included in the analysis. The effect of this was explored using the Stata
8
9 624 function steppedwedge,⁴³ which showed the statistical power would become 88.2%
10
11 625 (30% risk reduction) and 74.6% (25% risk reduction). It is anticipated that
12
13 626 unavailability of data and women asking to withdraw their data will be less than 1%.

14
15 627 *Proposed analyses*

16
17
18 628 For the binary primary and secondary outcomes, data will be analysed by
19
20 629 generalized linear mixed model with a random effect for hospital and fixed effects for
21
22 630 the intervention implementation and study time period. A site by intervention
23
24 631 interaction random effect will be included in the model and retained if it explains an
25
26 632 important proportion of the variability in outcomes. The primary analysis of data will
27
28 633 be on an intention to treat basis (the design of the trial means it is not possible to
29
30 634 determine individual patient /caregiver compliance with the intervention). An “on
31
32 635 treatment” variable will be calculated for which women will be grouped as active or
33
34 636 control according to when the intervention was actually implemented in their site,
35
36 637 instead of when the site was randomised to implement the intervention. The primary
37
38 638 outcome will be reanalysed in two sensitivity analyses. Firstly, we will perform the
39
40 639 analysis according to the actual timing of the implementation of the intervention
41
42 640 rather than the randomised timing of the intervention using the “on treatment”
43
44 641 classification. Secondly, we will perform the analysis in the subgroup of sites who
45
46 642 were deemed to have implemented the intervention effectively according to the
47
48 643 perception of the Principal Investigator at each site. The accuracy of this perception
49
50 644 will be confirmed with the findings of a site audit (details in Appendix 3). There will be
51
52 645 no attempt to correlate the impact of the intervention according to the results of the
53
54 646 site audit.

There are no planned imputations for missing data. However, if the missing data rate for smoking status during pregnancy is relatively high an imputation technique will be devised. The imputation method will be informed using smoking history at booking and age at delivery ⁴⁴. A pre-specified subgroup analysis will be performed for babies with and without congenital anomalies, and will be implemented by testing for an intervention by congenital anomaly interaction added to the generalised linear mixed model described above. No formal interim analyses for efficacy or safety will be performed. A full statistical analysis plan will be finalised prior to locking of the study database.

Qualitative Data

For the nested qualitative study, the data will be audio recorded and transcribed. The data will be coded thematically and an analytical framework developed to make sense of patient experience of fetal movement and the intervention and also health care providers' perspectives and experiences. NVivo will be utilised to support the analysis.

Process outcomes

The process outcomes being assessed by the (rates of induction of labour, number of women presenting with reduced fetal movements, interval between perceiving fetal movements and presenting to hospital) will be analysed using the same methods as for the main trial, with the exception of the continuous outcome (interval between perceiving fetal movements and presenting to hospital) which will be analysed using a normal linear mixed model.

ADVERSE EVENTS

This is not a Clinical Trial of an Investigational Medicinal Product (CTIMP) so adverse events will not be formally reported. Stillbirth and other measures of fetal and

maternal morbidity are outcomes of the study. The purpose of the intervention is to reduce such adverse events. Therefore, due to the low risks for this trial, a separate DMC is not required and the Trial Steering Committee (TSC) will cover any responsibilities normally allocated to a DMC. If considered necessary, the TSC may review unblinded data for the study, including morbidity and mortality indices. No other adverse event reporting will be undertaken.

679

TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

The trial will be coordinated by a Project Management Group, consisting of the grant holders and the Trial Manager. The Chief Investigator (JN) will lead the project management group. The Trial Manager will oversee the study and will be accountable to the Chief Investigator. A TSC will be established to oversee the conduct and progress of the trial. The terms of reference and a draft template for reporting will be ratified in one of the early meetings of the TSC.

Investigators and institutions involved in the study will permit trial related monitoring and audits on behalf of the co-sponsors (ACCORD: Academic and Clinical Central Office for Research & Development - Joint office for University of Edinburgh and NHS Lothian, Sponsor contact: ray.french@ed.ac.uk), research ethics committee (REC) review, and regulatory inspection(s). In the event of an audit or monitoring, the Investigator agrees to allow the representatives of the sponsor direct access to all study records and source documentation. In the event of regulatory inspection, the Investigator agrees to allow inspectors direct access to all study records and source documentation.

696

697

698 *Study monitoring and audit*

699 The sponsor determined that as no individual participants were recruited to the
700 intervention, and it was not a clinical trial of an investigational medicinal product
701 (CTIMP) no formal monitoring and audit was required.

702

703 *Good Clinical Practice and Ethical Conduct*

704 The study will be conducted in accordance with the principles of the research
705 governance framework operational and good clinical practice in the relevant country.
706 A favorable ethical opinion has been obtained from the Scotland A REC (Reference
707 13/SS/0001) and local research and development approval has been obtained prior
708 to commencement of the study.

709 Local study investigator(s) will be appointed to each site (or for small units, groups of
710 sites). S/he will be responsible for the overall conduct of the study at the site and
711 compliance with the protocol and any protocol amendments.

712

713 **STUDY CONDUCT RESPONSIBILITIES**

714 *Protocol amendments*

715 Any changes in research activity, except those necessary to remove an apparent,
716 immediate hazard to the participant in the case of an urgent safety measure, will be
717 reviewed and approved by the Chief Investigator and Sponsor. Amendments to the
718 protocol will be submitted in writing to the appropriate REC and local Research and
719 Development (R&D) department for approval prior to participants being enrolled into
720 an amended protocol.

721

722 *Protocol violations and deviations*

723 Investigators will not implement any deviation from the protocol without agreement
724 from the Chief Investigator and appropriate REC and R&D department approval
725 except where necessary to eliminate an immediate hazard to trial participants. In the
726 event that an Investigator needs to deviate from the protocol, the nature of and
727 reasons for the deviation will be recorded. If this necessitates a subsequent protocol
728 amendment, this will be submitted to the REC, and local R&D department for review
729 and approval if appropriate.

730 *Serious breach requirements*

731 A serious breach is one which is likely to effect to a significant degree (a) the safety
732 or physical or mental integrity of the participants of the trial; or b) the scientific value
733 of the trial. If a potential serious breach is identified by the Chief investigator,
734 Principal Investigator or delegates, the co-sponsors
735 (accord.seriousbreach@ed.ac.uk) will be notified within 24 hours. It will be the
736 responsibility of the co-sponsors to assess the impact of the breach on the scientific
737 value of the trial, to determine whether the incident constitutes a serious breach and,
738 if so, report it to the REC.

739 All violations will be assessed by the sponsor(s) to ascertain if they meet the criteria
740 for a serious breach. If the sponsor(s) deem the incident to be a violation that does
741 not constitute a serious breach from the protocol when identified, corrective and
742 preventative actions will be taken where appropriate and they will be recorded in file
743 notes, held within the TMF and ISF.

744 *Study record retention*

745 All study documentation will be kept for a minimum of 5 years from the protocol
746 defined end of study point. When the minimum retention period has elapsed, study
747 documentation will not be destroyed without permission from the sponsor.

748

749 *End of study*

750 The end of study date was finalised in the protocol after the study commenced; the
751 agreed end of study date is 31/12/2016. The Investigators and/or the trial steering
752 committee and/or the co-sponsor(s) have the right at any time to terminate the study
753 for clinical or administrative reasons.

754 The end of the study will be reported to the REC within 90 days, or 15 days if the
755 study is terminated prematurely. The Investigators will inform participants of the
756 premature study closure and ensure that the appropriate follow up is arranged for all
757 participants involved. A summary report of the study will be provided to the REC and
758 Regulatory Authority within 1 year of the end of the study.

759

760 **REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS**

761 Ownership of the data arising from this study resides with the study team. On
762 completion of the study, the study data will be analysed and tabulated, and a clinical
763 study report will be prepared in accordance with good clinical practice guidelines.
764 The clinical study report will be used as the basis for publication and presentation at
765 scientific meetings. Investigators have the right to publish orally or in writing the
766 results of the study. Summaries of results will also be made available to Investigators
767 for dissemination within their clinics (where appropriate and according to their
768 discretion).

769

770 **DISCUSSION**

771 The data provided by this study will inform the information given to women about
772 reduced fetal movements and their management when they present to maternity

773 services; which has been recurrently identified by Confidential Enquiries into
774 antepartum stillbirths as suboptimal^{26 27}. Data from the AFFIRM study will be able to
775 be compared to results from two other active studies which aim to improve mothers
776 awareness and reporting of reduced fetal movements. My Babies Movement
777 (ACTRN 12614000291684) is stepped-wedge cluster trial of a mobile phone
778 application to help women get to know their baby's movements, to be mindful of
779 movements every day and not to wait to report concerns to their maternity care
780 provider. The Mindfetalness study (NCT02865759) is a cluster trial of 39,000 women
781 randomised to routine antenatal care or the Mindfetalness brochure and website.⁴⁵
782 Women participating in the Mindfetalness process will spend 15 minutes each day
783 getting to know their babies movements and will specifically be encouraged to
784 contact their health provider if their perceive reduced fetal movements. This primary
785 outcome of this study is an Apgar score <7 at 5 minutes; stillbirth and perinatal
786 deaths will be recorded as tertiary endpoints of this study.⁴⁵ These large studies will
787 provide much needed robust evidence to determine whether increased maternal
788 awareness of reduced fetal movements combined with a standardised management
789 protocol to identify acute or chronic fetal compromise can reduce stillbirth³².

790

791 **PEER REVIEW**

792 This project has been peer reviewed internally, and was externally peer reviewed
793 during the process of securing funding from the Chief Scientist's Office of the
794 Scottish Government, Tommy's and Sands.

795

796 **FUNDING**

797 The AFFIRM study is investigator initiated and funded by Chief Scientist Office,
798 Scottish Government (CZH/4/882), Tommy's and Sands, the Stillbirth and Neonatal
799 Death Charity. CJW was supported in this work by NHS Lothian via the Edinburgh

1
2
3 800 Clinical Trials Unit. AEPH is supported by a Clinician Scientist fellowship from the
4
5 801 National Institute for Health Research (NIHR; CS-2013-009). This protocol presents
6
7 802 independent research funded by the National Institute for Health Research (NIHR).
8
9 803 The views expressed are those of the author(s) and not necessarily those of the
10
11 804 NHS, the NIHR or the Department of Health.
12
13 805

14 15 806 **ACKNOWLEDGEMENTS**

16
17 807 The authors would like to acknowledge the support of Perinatal Ireland and Dr Mary
18
19 808 Higgins (University College Dublin, National Maternity Hospital, Dublin).
20
21 809

22 23 810 **CONTRIBUTIONS**

24
25 811 Contributors AEPH, CJW, SJES, CJC, SCB, MRD, SW and JEN were involved in
26
27 812 developing the trial design. AEPH, CJW, SJES, AR and JEN were involved in
28
29 813 drafting and revision of the article. CJW and AR were involved in drafting the
30
31 814 statistical aspects of the protocol. JS provided feedback on behalf of a stakeholder
32
33 815 organisation. AEPH, CJW, SJES, CJC, SCB, JFF, MG, AH, FMM, EM, AR, MRD, JS,
34
35 816 SW and JEN were involved in preparing the overall study design. AEPH, JEN and
36
37 817 MRD prepared education videos for online training. AEPH, SJES, SJS, MG, AH,
38
39 818 FMM and JEN facilitated recruitment of sites. AEPH, CJW, SJES, CJC, SCB, JFF,
40
41 819 MG, AH, FMM, EM, AR, MRD, JS, SW and JEN will be involved in the collection,
42
43 820 management, analysis and interpretation of data and final writing of the trial report.
44
45 821

46 47 822 **COMPETING INTERESTS**

48
49 823 None declared.
50
51
52
53
54
55
56
57
58
59
60

824 **ABBREVIATIONS**

825	ACCORD	Academic and Clinical Central Office for Research & Development -
826		Joint office for University of Edinburgh and NHS Lothian
827	BMI	Body Mass Index
828	CTG	Cardiotocograph
829	CTIMP	Clinical Trial of an Investigational Medicinal Product
830	ECTU	Edinburgh Clinical Trials Unit
831	FGR	Fetal growth restriction
832	MHRA	Medicines and Healthcare products Regulatory Agency
833	NICE	National Institute for Health and Social Care Excellence
834	NIHR	National Institute for Health Research
835	NIMATS	Northern Ireland Maternity Statistics database
836	NRPS	National Perinatal Reporting System
837	ONS	Office of National Statistics
838	PSANZ	Perinatal Society of Australia and New Zealand
839	RCOG	Royal College of Obstetricians and Gynaecologists
840	R&D	Research and Development
841	REC	Research Ethics Committee
842	RFM	Reduced Fetal Movements
843	SPIMMR	Scottish Perinatal and Infant Mortality and Morbidity Report
844	TMF	Trial Master File
845	TSC	Trial Steering Committee
846	WHO	World Health Organisation

847

848

REFERENCES

1. Curtis L, Burns A. Unit Costs of Health and Social Care 2015 Canterbury: Personal Social Services Research Unit, The University of Kent, 2015.
2. Warland J, O'Brien LM, Heazell AE, Mitchell EA. An international internet survey of the experiences of 1,714 mothers with a late stillbirth: the STARS cohort study. *BMC pregnancy and childbirth* 2015;15:172.
3. Flenady V, Koopmans L, Middleton P, Froen JF, Smith GC, Gibbons K, et al. Major risk factors for stillbirth in high-income countries: a systematic review and meta-analysis. *Lancet* 2011;377(9774):1331-40.
4. Manktelow BM, Smith LK, Seaton SE, Hyman-Taylor P, Kurinczuk JJ, Field DJ, et al. Perinatal Mortality Surveillance Report - UK Perinatal Deaths for births from January to December 2014. Leicester:: The Infant Mortality and Morbidity Group, Department of Health Sciences, University of Leicester., 2016.
5. Sadovsky E, Polishuk WZ. Fetal movements in utero: nature, assessment, prognostic value, timing of delivery. *Obstet Gynecol* 1977;50(1):49-55.
6. Flenady V, Middleton P, Smith GC, Duke W, Erwich JJ, Khong TY, et al. Stillbirths: the way forward in high-income countries. *Lancet* 2011;377(9778):1703-17.
7. Heazell AE, Whitworth MK, Whitcombe J, Glover SW, Bevan C, Brewin J, et al. Research priorities for stillbirth: process overview and results from UK Stillbirth Priority Setting Partnership. *Ultrasound Obstet Gynecol* 2015;46(6):641-7.
8. Heazell AE, Froen JF. Methods of fetal movement counting and the detection of fetal compromise. *J Obstet Gynaecol* 2008;28(2):147-54.
9. Stacey T, Thompson JM, Mitchell EA, Ekeroma AJ, Zuccollo JM, McCowan LM. The Auckland Stillbirth study, a case-control study exploring modifiable risk factors for third trimester stillbirth: methods and rationale. *The Australian & New Zealand journal of obstetrics & gynaecology* 2011;51(1):3-8.

1
2
3 877 10. Ptacek I, Sebire NJ, Man JA, Brownbill P, Heazell AE. Systematic review of
4
5 878 placental pathology reported in association with stillbirth. *Placenta*
6
7 879 2014;35(8):552-62.
8
9 880 11. Warrander LK, Heazell AE. Identifying placental dysfunction in women with
10
11 881 reduced fetal movements can be used to predict patients at increased risk of
12
13 882 pregnancy complications. *Medical hypotheses* 2011;76(1):17-20.
14
15 883 12. Vintzileos AM, Fleming AD, Scorza WE, Wolf EJ, Balducci J, Campbell WA, et al.
16
17 884 Relationship between fetal biophysical activities and umbilical cord blood gas
18
19 885 values. *Am J Obstet Gynecol* 1991;165(3):707-13.
20
21 886 13. Warrander LK, Batra G, Bernatavicius G, Greenwood SL, Dutton P, Jones RL, et
22
23 887 al. Maternal perception of reduced fetal movements is associated with altered
24
25 888 placental structure and function. *PloS one* 2012;7(4):e34851.
26
27 889 14. Winje BA, Roald B, Kristensen NP, Froen JF. Placental pathology in pregnancies
28
29 890 with maternally perceived decreased fetal movement--a population-based
30
31 891 nested case-cohort study. *PloS one* 2012;7(6):e39259.
32
33 892 15. Holm Tveit JV, Saastad E, Stray-Pedersen B, Bordahl PE, Froen JF. Maternal
34
35 893 characteristics and pregnancy outcomes in women presenting with decreased
36
37 894 fetal movements in late pregnancy. *Acta Obstet Gynecol Scand*
38
39 895 2009;88(12):1345-51.
40
41 896 16. Healthcare Improvement Scotland. Scottish Perinatal and Infant Mortality and
42
43 897 Morbidity Report 2010. Edinburgh: Healthcare Improvement Scotland, 2012.
44
45 898 17. Gardosi J, Kady SM, McGeown P, Francis A, Tonks A. Classification of stillbirth
46
47 899 by relevant condition at death (ReCoDe): population based cohort study. *BMJ*
48
49 900 (*Clinical research ed* 2005;331(7525):1113-7.
50
51 901 18. Saastad E, Winje BA, Stray Pedersen B, Froen JF. Fetal movement counting
52
53 902 improved identification of fetal growth restriction and perinatal outcomes--a
54
55 903 multi-centre, randomized, controlled trial. *PloS one* 2011;6(12):e28482.
56
57
58
59
60

- 1
2
3 904 19. Mangesi L, Hofmeyr GJ, Smith V, Smyth RM. Fetal movement counting for
4
5 905 assessment of fetal wellbeing. *Cochrane Database Syst Rev*
6
7 906 2015(10):CD004909.
8
9 907 20. Grant A, Elbourne D, Valentin L, Alexander S. Routine formal fetal movement
10
11 908 counting and risk of antepartum late death in normally formed singletons.
12
13 909 *Lancet* 1989;2(8659):345-9.
14
15 910 21. National Institute for Health and Clinical Excellence. Clinical Guideline 62 -
16
17 911 Antenatal care: routine care for the healthy pregnant woman. London: National
18
19 912 Institute for Health and Clinical Excellence, 2008.
20
21 913 22. Sergent F, Lefevre A, Verspyck E, Marpeau L. Decreased fetal movements in the
22
23 914 third trimester: what to do? *Gynecol Obstet Fertil* 2005;33(11):861-9.
24
25 915 23. Froen JF, Heazell AE, Tveit JV, Saastad E, Fretts RC, Flenady V. Fetal
26
27 916 movement assessment. *Seminars in perinatology* 2008;32(4):243-6.
28
29 917 24. Saastad E, Vangen S, Froen JF. Suboptimal care in stillbirths - a retrospective
30
31 918 audit study. *Acta Obstet Gynecol Scand* 2007;86(4):444-50.
32
33 919 25. Froen JF, Arnestad M, Frey K, Vege A, Saugstad OD, Stray-Pedersen B. Risk
34
35 920 factors for sudden intrauterine unexplained death: epidemiologic
36
37 921 characteristics of singleton cases in Oslo, Norway, 1986-1995. *Am J Obstet*
38
39 922 *Gynecol* 2001;184(4):694-702.
40
41 923 26. Confidential Enquiry into Stillbirths and Deaths in Infancy. 8th Annual Report, 1
42
43 924 January–31 December 1999. London: Maternal and Child Health Research
44
45 925 Consortium, 2001.
46
47 926 27. Manktelow BM, Smith LK, Evans TA, Hyman-Taylor P, Kurinczuk JJ, Field DJ, et
48
49 927 al. Perinatal Mortality Surveillance Report - UK Perinatal Deaths for births
50
51 928 from January to December 2013. . Leicester:: The Infant Mortality and
52
53 929 Morbidity Group, Department of Health Sciences, University of Leicester.,
54
55 930 2015.
56
57
58
59
60

28. Linde A, Pettersson K, Radestad I. Women's Experiences of Fetal Movements before the Confirmation of Fetal Death--Contractions Misinterpreted as Fetal Movement. *Birth* 2015;42(2):189-94.

29. Preston S, Mahomed K, Chadha Y, Flenady V, Gardener G, MacPhail J, et al. Clinical practice guideline for the management of women who report decreased fetal movements. Brisbane,: Australia and New Zealand Stillbirth Alliance, 2010.

30. Royal College Of Obstetricians and Gynaecologists. Management of Reduced Fetal Movements. London: RCOG, 2011.

31. Tveit JV, Saastad E, Stray-Pedersen B, Bordahl PE, Flenady V, Fretts R, et al. Reduction of late stillbirth with the introduction of fetal movement information and guidelines - a clinical quality improvement. *BMC pregnancy and childbirth* 2009;9:32.

32. Hofmeyr GJ, Novikova N. Management of reported decreased fetal movements for improving pregnancy outcomes. *Cochrane Database Syst Rev* 2012;4:CD009148.

33. Froen JF, Tveit JV, Saastad E, Bordahl PE, Stray-Pedersen B, Heazell AE, et al. Management of decreased fetal movements. *Seminars in perinatology* 2008;32(4):307-11.

34. Dutton PJ, Warrander LK, Roberts SA, Bernatavicius G, Byrd LM, Gaze D, et al. Predictors of poor perinatal outcome following maternal perception of reduced fetal movements--a prospective cohort study. *PloS one* 2012;7(7):e39784.

35. Royal College Of Obstetricians and Gynaecologists. The Investigation And Management Of The Small-For-Gestational-Age Fetus. London: RCOG, 2013.

36. Heazell AE, Green M, Wright C, Flenady V, Froen JF. Midwives' and obstetricians' knowledge and management of women presenting with decreased fetal movements. *Acta Obstet Gynecol Scand* 2008;87(3):331-9.

37. NHS England. Saving Babies' Lives - A care bundle for reducing stillbirth. Leeds: Acute Care Policy Unit, 2015.
38. Tveit JV, Saastad E, Stray-Pedersen B, Bordahl PE, Flenady V, Fretts R, et al. Correction: Reduction of late stillbirth with the introduction of fetal movement information and guidelines - a clinical quality improvement. *BMC pregnancy and childbirth* 2010;10:49.
39. Winje BA, Wojcieszek AM, Gonzalez-Angulo LY, Teoh Z, Norman J, Froen JF, et al. Interventions to enhance maternal awareness of decreased fetal movement: a systematic review. *Bjog* 2016;123(6):886-98.
40. Mitchell ML. Fetal brain to liver weight ratio as a measure of intrauterine growth retardation: analysis of 182 stillborn autopsies. *Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc* 2001;14(1):14-9.
41. Barbaux S, Erwich JJ, Favaron PO, Gil S, Gallot D, Golos TG, et al. IFPA meeting 2014 workshop report: Animal models to study pregnancy pathologies; new approaches to study human placental exposure to xenobiotics; biomarkers of pregnancy pathologies; placental genetics and epigenetics; the placenta and stillbirth and fetal growth restriction. *Placenta* 2015;36 Suppl 1:S5-10.
42. Coleman SJ, Gerza L, Jones CJ, Sibley CP, Aplin JD, Heazell AE. Syncytial nuclear aggregates in normal placenta show increased nuclear condensation, but apoptosis and cytoskeletal redistribution are uncommon. *Placenta* 2013;34(5):449-55.
43. Hemming K, Girling A. A menu-driven facility for power and detectable-difference calculations in stepped-wedge cluster-randomized trials. *The Stata Journal* 2014;14:363-80.

1
2
3 985 44. Jokhan S, Whitworth MK, Jones F, Saunders A, Heazell AE. Evaluation of the
4
5 986 quality of guidelines for the management of reduced fetal movements in UK
6
7 987 maternity units. *BMC pregnancy and childbirth* 2015;15:54.
8
9 988 45. Radestad I, Akselsson A, Georgsson S, Lindgren H, Pettersson K, Steineck G.
10
11 989 Rationale, study protocol and the cluster randomization process in a
12
13 990 controlled trial including 40,000 women investigating the effects of
14
15 991 mindfetalness. *Sexual & reproductive healthcare : official journal of the*
16
17 992 *Swedish Association of Midwives* 2016;10:56-61.
18
19 993
20
21 994
22
23
24 995
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

996 **FIGURE LEGENDS**

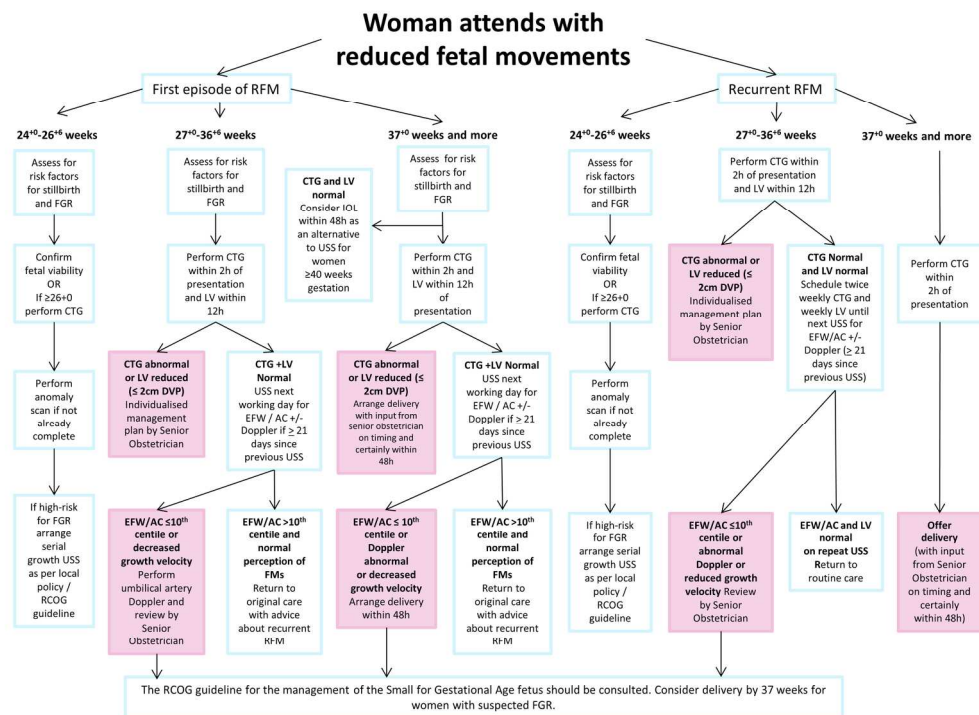
997 Figure 1 - Stepped wedge design. The shaded areas (both light and dark) indicate
998 periods in which the interventions are being implemented. The lighter areas indicate
999 the “transition” period during which data will not be collected for the control or
1000 intervention group. The order in which hospital groupings implement the interventions
1001 will be determined via randomization.

1002 Figure 2 – Flow chart for the management of women presenting with reduced fetal
1003 movements for sites implementing the AFFIRM study. Abbreviations: AC - abdominal
1004 circumference, CTG- cardiotocograph, DVP - deepest vertical pool, EFW - estimated
1005 fetal weight, FGR - fetal growth restriction, LV - liquor volume, RFM - reduced fetal
1006 movement, USS - ultrasound scan.

Hospital groupings	Months since Start of Trial								
	1-4	5-8	9-12	13-16	17-20	21-24	25-28	29-32	33-36
1-3									
4-6									
7-9									
10-12									
13-15									
16-18									
19-21									
22-24									

Stepped wedge design. The shaded areas (both light and dark) indicate periods in which the interventions are being implemented. The lighter areas indicate the “transition” period during which data will not be collected for the control or intervention group. The order in which hospital groupings implement the interventions will be determined via randomization.

190x142mm (300 x 300 DPI)



Flow chart for the management of women presenting with reduced fetal movements for sites implementing the AFFIRM study. Abbreviations: AC - abdominal circumference, CTG- cardiotocograph, DVP - deepest vertical pool, EFW - estimated fetal weight, FGR - fetal growth restriction, LV - liquor volume, RFM - reduced fetal movement, USS - ultrasound scan.

190x142mm (300 x 300 DPI)

WHO TO CONTACT IF YOU ARE CONCERNED:
(space for sticky with local contact information)



APS Group Scotland
DPPAS33137
Version 3 March 2015



In touch with
YOUR BABY

A guide to your baby's
movements during
pregnancy



For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>

**Why are my baby's
movements important?**

**Why are we asking women
to get to know their baby's
movements?**

One of the easiest ways to tell if your baby is healthy is to be aware of how much he or she is moving. Every baby is different and we are asking women to take time to become familiar with their baby's own individual pattern of movements. A reduction or change in **your** baby's movements is what is important.

**What can affect my baby's
movements?**

You are less likely to be aware of your baby's movements when active or busy. Some drugs e.g. strong pain relief or sedatives can get into an unborn baby's circulation and affect the movements. Alcohol and smoking (active and passive smoking) may also affect the baby.

**Why are my baby's
movements important?**

If you notice your baby is moving less than usual, or the pattern of movements has changed, this could be the first sign that your baby may not be well or is not growing properly in the womb. Research has shown that a reduction in the baby's movements may indicate an increased risk of stillbirth. You may hear your midwife or doctor referring to 'reduced fetal movement', or RFM for short.

What are the risks of stillbirth?

Stillbirth affects one in 200 babies after 24 weeks gestation and is one of the most common of the serious complications of pregnancy, affecting the lives of around 4,000 families every year in the UK.

One of the easiest ways to tell if your baby is healthy is to see how much he or she is moving. This booklet tells you what to look out for during your pregnancy.

Every baby is different. It is good to get to know your baby's own movements and the pattern of their sleeping and waking and report to us if you notice a reduction in these movements.



18-24
WEEKS



Most women begin to feel their baby move between 18-24 weeks. At first it may feel like 'bubbles', 'flutterings' or 'like trapped wind'. These are often very short and stop and start. It might take you a little while to be sure what you are feeling. But you will soon get to know the feelings. If this is your second baby, you will know what to look out for and may recognise your baby moving sooner.

Everyone is different when it comes to their movements. There are many reasons you might not feel movements as early as you expect. This includes your body weight, the position of your baby and the location of your placenta. What is important is your baby is growing well. Your midwife will be able to discuss this with you further at your 22 week check.

Try to get to know the times of the day when you are most likely to feel your baby move.



24-36
WEEKS



You will have your own way of describing your baby's own movements. Women often describe their baby's movements as 'rolling', 'kicking', 'pushing', 'jabs', 'elbowing' and 'stretches'.

Between 24-36 weeks you will start to recognise your baby's movements more quickly and become more used to the feeling. It is usually easier to feel your baby's movements when you are lying down, e.g. at night time. It is harder to feel your baby move when you are on your feet and moving around.

Try to get to know the times of the day you are most likely to feel your baby move. This will help you to know if he or she is moving less than normal or if movements have stopped.

Occasionally your baby will get hiccups. These do not count as movements. If you are unsure what you should expect when your baby hiccups, speak to your midwife.



Appendix 2 - Audit of compliance with AFFIRM protocol

Compliance with the AFFIRM management protocol (the management plan for women presenting with reduced fetal movement) will be determined by to means:

A) Telephone / email contact with Principal Investigators at each site to determine which aspects of the AFFIRM protocol have been implemented effectively. This will involve email contact with Principal Investigators to alert them to the request for information, an email detailing the information required, and then a phone call to elicit the information (unless it had already been supplied). Investigators will be asked which of the following elements they had implemented: issuing leaflets to all pregnant women, cardiotocography within 2 hours of presentation, measurement of amniotic fluid volume within 12 hours of presentation, growth scan by the next working day for all women presenting with reduced fetal movement (and who had not had a growth scan within the last three weeks, or who were not being induced within 48 hours), and induction of labour within 48 hours for women presenting with recurrent reduced fetal movement at or after 37 weeks gestation. “Effective implementation” was defined as the above management for 4/5 of these elements for 80% or more of the time.

B) An audit to determine whether the perception of the site Principal Investigator is supported by review of actual decision making will be performed for the following elements: cardiotocography within 2 hours of presentation, measurement of amniotic fluid volume within 12 hours of presentation, growth scan by the next working day for all women presenting with reduced fetal movement (and who had not had a growth scan within the last three weeks, or who were not being induced within 48 hours), and induction of labour within 48 hours for women presenting with recurrent reduced fetal movement at or after 37 weeks gestation.

This will be conducted by asking sites to complete an audit of the management of all women presenting with reduced fetal movement over the course of one calendar month. Sites will be asked to complete an audit form for each participant. The audit form template (see below) has been generated by the central

AFFIRM study team; anonymized forms will be analysed centrally. There will not be an attempt to corroborate Principal Investigator perception of the proportion of women who were given leaflets, nor will there be any attempt to incorporate the proportion of staff who had completed the e-learning package into analysis of whether any specific site has implemented the intervention or not.

For peer review only

Compliance with AFFIRM reduced fetal movements protocol, One month data collection AUDIT [Month & Year] Unit name: [Name of Hospital]

If you assess a woman with reduced fetal movements (RFM), please complete the questions below. Do not worry if the woman has been seen in other areas of the hospital by other staff, we would rather have multiple reports for the same woman than miss episodes of RFM.

INSERT Patient Sticker (or WRITE name and CHI /NHS number)				AREA WHERE SEEN (CIRCLE) Triage / Labour ward / Day Assessment Unit (DAU) Other (specify area i.e. antenatal ward): _____							
Date and time of presentation with reduced fetal movements.	DATE: ____/____/____ TIME ____:____ am / pm				GESTATION AND EDD:	____ WEEKS ____ DAYS EDD: _____					
Referred by (TICK BOX):	Self	Community Midwife	GP	ANC	Triage	DAU	Other (specify: _____)				
What was the primary reason for attending/phoning? (TICK BOX):	Reduced Fetal Movements				Other (specify: _____)						
How many times has the woman attended before this visit, with RFM? (TICK BOX):	None – first attendance		Once previously		Unknown	Multiple times (please provide the gestation at each presentation i.e. 30+6)	1	2	3	4	5
What was the time interval from the woman first being aware of reduced fetal movements and attending the hospital (in hours)?						HOURS: _____					
Has she been given a leaflet “Your baby’s movements in pregnancy”? (TICK BOX):	Yes – she already has one		Yes – I have given one to her today			Locally Created Leaflet Given		NO			
Has this woman had a growth USS in this pregnancy? (TICK BOX):	No, she has not had a growth scan		Yes, within the last 3 weeks (date of scan): DATE: ____/____/____			Yes, but more than 3 weeks ago (date of scan): DATE: ____/____/____					

CONTINUATION: NHS/ CHI NUMBER:

Are any of the following risk factors for Fetal growth restriction present (CIRCLE all that apply)?							
Age ≥40 or ≤16	Smoker ≥20cpd	Known or suspected growth restriction	Congenital anomaly	Raised BP (essential hypertension, pre-eclampsia or pregnancy induced hypertension)	Previous pre-eclampsia	Diabetes or gestational diabetes	Previous FGR or stillbirth
What investigations were conducted during this episode of reduced fetal movement?							
Please record below the date and time that these investigations were completed or indicate if not performed.						Please provide the results (CIRCLE):	
CTG	Not performed <input type="checkbox"/>	DATE: __/__/____	TIME: ____:____ am/pm	Normal / Suspicious / Pathological			
		<u>Computerised CTG</u> : YES / NO (CIRCLE)					
Liquor volume assessment on scan	Not performed <input type="checkbox"/>	DATE: __/__/____	TIME: ____:____ am/pm	Normal / Reduced / Increased			
Growth scan	Not performed <input type="checkbox"/>	DATE: __/__/____	TIME: ____:____ am/pm	Normal / EFW < 10 th centile/ AC < 10 th centile / EFW and AC < 10 th centile			
Umbilical Artery Doppler	Not performed <input type="checkbox"/>	DATE: __/__/____	TIME: ____:____ am/pm	Normal/.> 95 th centile/absent EDF/reversed EDF			
MCA Doppler	Not performed <input type="checkbox"/>	DATE: __/__/____	TIME: ____:____ am/pm	Normal/<5 th centile			
DELIVERY METHOD (If available)							
Was the woman offered induction of labour	YES / NO (CIRCLE) IF Yes, please provide date, time and method of the induction:			DATE: ____/____/____ TIME: ____:____ am/pm			
Was the woman offered elective caesarean section as a result of the reduced fetal movement?	YES / NO (CIRCLE) IF Yes, please provide date, time and reason:			DATE: ____/____/____ TIME: ____:____ am/pm Please provide the reason for the elective Caesarean section:			



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page 4
	2b	All items from the World Health Organization Trial Registration Data Set	Included throughout protocol
Protocol version	3	Date and version identifier	Page 4
Funding	4	Sources and types of financial, material, and other support	Pages 31-32
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Names and affiliations Page 1 and 2; Contributions Page 32
	5b	Name and contact information for the trial sponsor	Page 27
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Not applicable

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	___Page 27___
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	__Pages 5-12__
	6b	Explanation for choice of comparators	__Pages 8-10__
Objectives	7	Specific objectives or hypotheses	__Page 12__
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	__Pages 15-16 and Figure 1__
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (e.g., community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	__Pages 15 & 24__
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	__Pages 16-17__
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	__Pages 19-20 and Figure 2__
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	__Not applicable in AFFIRM trial__
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	__Pages 19-20__
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	__Not applicable__

1				
2				
3	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	__Pages 13-14__
4				
5				
6				
7				
8	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	__Randomisation by site explained in Figure 1 and Pages 18-19__
9				
10				
11				
12				
13	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	__Pages 23-25__
14				
15				
16				
17	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	__Page 23__
18				
19	Methods: Assignment of interventions (for controlled trials)			
20				
21	Allocation:			
22				
23	Sequence generation	16a	Method of generating the allocation sequence (e.g., computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	__Pages 18-19__
24				
25				
26				
27				
28				
29	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	__Page 19__
30				
31				
32				
33	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	__Page 19__
34				
35				
36	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	__Page 19__
37				
38				
39		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	__Not applicable in AFFIRM study__
40				
41				
42				
43				
44				
45				
46				
47				
48				
49				

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	__Pages 20-23__
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	__Not applicable__
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	__Pages 21-22__
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	__Pages 25-26__
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	__Pages 25-26__
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	__Pages 25-26__

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	_DMC not required, explanation Pg 27__
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	__Pages 20, 28-29__
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	__Pages 26-27__
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	__Page 15__

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	__Page 28__
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	__Page 28__
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	__Page 28__
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	__Not applicable__
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	__Pages 21-22__
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	__Page 32__
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	__Page 30__
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	__Page 27__
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	__Page 30__
	31b	Authorship eligibility guidelines and any intended use of professional writers	__Page 31__
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	__Not applicable__

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_Not Applicable__
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_Not Applicable__

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](#)" license.